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SYMPOSIUM ON GASTROINTESTINAL BLEEDING*

DIAGNOSTIC AND THERAPEUTIC CONSIDERATIONS OF GASTROINTESTINAL BLEEDING

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ANY consideration of bleeding from the gastrointestinal tract holds the immediate implication that the problem may be either medical or surgical. This is of primary importance and must never be forgotten, either in the discussion of the general problem or in the making of decisions in the individual case. Because of the possible necessity of surgical intervention, gastrointestinal hemorrhage must invariably be considered from three distinct points of view. It must be thought of in terms of the actual site of the bleeding, which implies the necessity for accurate diagnosis whenever possible. The mechanism underlying the hemorrhage must also be carefully evaluated so that proper therapeutic measures may be decided on. The third consideration is the condition of the patient who is bleeding. Even before diagnostic or definitive therapeutic measures are undertaken, a decision must be made regarding the urgency of the situation in terms of shock and circulatory collapse.

A clear differentiation is needed between abrupt hemorrhage of shock proportions and minor oozing that, in the long run, may lead to more or less serious grades of anemia but is not an immediate threat to life. In major acute episodes the immediate concern is the safety of the patient. Even under the pressure of exsanguinating hemorrhage, however, selected diagnostic procedures are indicated if successful definitive measures are to be carried out. At the same time, a knowledge of the hazards involved is essential in arriving at a final decision concerning therapy, whether medical or surgical.

Any attempt to classify digestive-tract bleeding on the basis of the site of the lesion must be founded on a knowledge of anatomic and pathologic abnormalities encountered at various levels of the alimentary canal. This can be divided roughly into three segments: from the pharynx to the ligament of Treitz, from the ligament of Treitz to the ileocecal valve and from the ileocecal valve to the anus. A fourth possible subdivision includes the anal canal only.

In the upper segment — namely, the esophagus, stomach and duodenum — bleeding is usually associated with the vomiting of coffee-grounds material, inky-black fluid or frank blood. Even with esophageal bleeding, however, blood may not be vomited, and hemorrhage may be suspected only because of tarry stools. Melena is the rule in upper gastrointestinal-tract bleeding, but it must not be forgotten that feces containing currant-jelly-like, deep-reddish material may be encountered if the hemorrhage is brisk and the peristaltic rate rapid.

Esophageal bleeding is due either to varices or to cancer in most cases. Bleeding infrequently occurs from varices that are located in the fundus of the stomach rather than in the esophagus. Bleeding from esophageal ulcer can occur, but it is rare.

Gastroduodenal hemorrhage is usually due to peptic ulcers, the great majority of which are located in the first portion of the duodenum. Benign ulcers that bleed may occur, however, anywhere from the cardiac end of the stomach to the ligament of Treitz, and can be identified only by careful roentgenologic studies. Cancer of the stomach causes massive hemorrhage only occasionally, but it can do so. Less frequent causes of bleeding from the stomach are erosive gastritis, generalized or localized as in a diaphragmatic hernia, benign tumors that have become ulcerated and rare tumors, such as leiomyosarcomas, fibromas and neuromas. Carcinoma of the duodenum is extremely infrequent, but does occur and may cause bleeding. Duodenal leiomyosarcomas are more frequent and may underlie a serious anemia or may cause a fairly brisk hemorrhage.

It should be emphasized that gastritis alone is occasionally the source of an exsanguinating loss of

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blood. It is also essential to remember that massive hemorrhage from ulcer is frequently unassociated with pain.

In the midsegment — the jejunum and ileum — massive hemorrhage is rather rare, but anemia from chronic loss of relatively small amounts of blood is not infrequent. Hematemesis does not occur from lesions below the ligament of Treitz, except in the presence of frank obstruction with fecal vomiting, or in association with an ulcerated lesion near the stoma of a gastroenterostomy. Dependent on the peristaltic rate, bleeding from the midsegment may result in either tarry stools or fresh, blood-stained feces.

Acute bleeding may result from frank ulceration, such as that encountered in typhoid fever, or from a single ulcer, notably that associated with a Meckel's diverticulum, which is usually, but not invariably, seen in children and young adults. Tumors, unless pedunculated and therefore subject to torsion, do not, as a rule, cause massive bleeding. Rather, they result in a gradually progressive anemia due to ulceration and oozing. Carcinomas, leiomyosarcomas, lymphomas and benign polypoid tumors, such as simple adenomas and lipomas, cause bleeding that may or may not be associated with the clinical picture of intussusception. With modern methods of roentgenologic examination, the site of the bleeding in the small intestine is often demonstrated if its approximate location is suspected. Other sources of moderate bleeding in this portion of the bowel are the granulomatous processes, notably tuberculosis and regional enteritis, both of which tend to be located in the vicinity of the ileocecal valve. Acute infectious processes, such as food poisoning and gastroenteritis due to what is popularly known as "intestinal grippe," may cause moderate bleeding from the small intestine.

Bleeding in the colon, which may be due to a wide variety of conditions, is demonstrated by the passage of varying amounts of fresh or slightly altered blood in the stools. Cancer must be suspected first, last and always in the presence of colonic bleeding. Until it is eliminated no other diagnosis should be considered. Carcinoma of the colon may cause gross, shock-producing hemorrhage, but as a rule effects a more chronic blood loss resulting in an anemia that may be serious. Other tumors are the source of intermittent fresh bleeding. Of these, in the absence of signs of serious disease, the adenomatous polyp, which is always potentially cancerous, should be the first suspect.

If carcinoma and adenoma can be ruled out, colonic bleeding should suggest the possibility of one of the various forms of ulcerative colitis. If the onset is abrupt, amebic and bacillary dysentery must be eliminated by appropriate diagnostic measures. Tuberculous colitis and idiopathic ulcerative colitis are usually more insidious in onset and more chronic in their clinical manifestations but, like the dysenteries, are accompanied by diarrhea.

An important cause of serious colonic bleeding may be the end result of damage to the bowel secondary to heavy irradiation of pelvic tumors. Rarely, bright-red blood may be passed by rectum from areas of diverticulitis or in the presence of mucous colitis. Such a possibility should never be considered until all other sources of bleeding have been eliminated, and even then it should be accepted only with extreme skepticism.

I have enumerated many of the possible sources of gastrointestinal hemorrhage on the basis of a strict anatomic or pathologic location. It is equally necessary to visualize the type of mechanism involved in the hemorrhage. This is particularly vital in arriving at the details of therapeutic management involved in any given case. For example, the bleeding from a peptic ulcer is essentially arterial and therefore has a graver prognosis at the age of sixty than at thirty, owing to the fact that the arteries are less elastic, contract less well and, in addition, may carry a high systolic pressure. Bleeding from varices, on the other hand, is from a thin-walled, relatively atonic vessel that is easily traumatized and has little contractility but has great possibilities of thrombosis and obliteration by clot formation. The hemorrhage secondary to a mesenteric-artery thrombosis carries with it the added threat of gangrene of the bowel and therefore the possible necessity of emergency surgery.

Capillary bleeding may occur over a large enough area to provide an immediate threat to life, although, as a rule, it is of lesser magnitude. The bleeding from gastritis, either diffuse or localized, and that encountered in idiopathic ulcerative colitis are usually of capillary origin. Similarly, in bacillary dysentery, bleeding is the result of tiny, superficial mucosal erosions involving capillary loops. In diverticulitis and so-called "mucous colitis," the infrequent episode of bleeding is probably due to a local inflammatory process with involvement of a small vessel. In hemorrhage secondary to postradiation lesions of the sigmoid or ileum, the bleeding comes from telangiectatic areas similar to those noted in the skin following x-ray burns but because of the larger vessels involved, may be of greater degree than that usually noted in capillary oozing and may require local surgical resection.

Significant hemorrhage, essentially of capillary origin, may be due to general hemorrhagic disturbances associated with the thrombocytopenia encountered in the leukemias and bone-marrow aplasias, or with the prothrombin lack associated with serious hepatic disease or chronic diarrhea. Vitamin C deficiency may provide the basis for blood loss from the digestive tract from capillary oozing. Similarly, serious capillary bleeding may be due to hemophilia, but this is only a manifestation of a general physiologic disorder affecting more than the

alimentary canal. Specific toxic agents such as emetine and radium may cause bloody diarrhea as a result of damage to the capillaries or bone marrow. Not infrequently, similar symptoms occur in uremia, but only as a terminal event.

It is thus obvious that a proper evaluation of gastrointestinal bleeding must include exact knowledge of the site of blood loss and, in addition, an understanding of the mechanism involved. Without such an evaluation, therapeutic measures cannot be properly carried out. It may be added that failure to obtain sufficient information to cover both requirements constitutes a failure of medical management and cannot be condoned. Furthermore, it is essential to stress the fact that obvious sources of bleeding may not provide the actual explanation for hemorrhagic episodes. Much too often the demonstration of hemorrhoids or anal fissures is accepted as a satisfactory explanation of rectal bleeding when the true cause is a carcinoma of the bowel or a serious ulcerative process.

To obtain adequate information regarding the source and nature of gastrointestinal bleeding, carefully selected diagnostic procedures must be carried out. If the hemorrhage is a massive one and shock is present or imminent, such measures must of necessity be brief and to the point. They must not interfere with the immediate treatment needed for combating acute blood loss. Blood volume must be restored at once by transfusions of whole blood, but this must not be administered so rapidly as to cause a sharp rise in blood pressure. Gravity-drip, regulated transfusions are the measure of choice, and should be used until shock is controlled. Plasma, which is of much less value than whole blood, should be used only when blood is unavailable. An important reason for avoiding the use of pooled plasma, in addition to the fact that it does not replace hemoglobin and prothrombin, is that it carries a definite risk of transmitting the virus of infectious hepatitis. Physiologic saline solution should be used only as a temporary expedient until whole blood can be obtained. In the presence of protein or albumin lack, such as that occurring in depleted patients or in serious hepatic disease, the use of saline solution may precipitate the appearance of pulmonary edema or generalized tissue edema.

During the period of shock therapy, certain valuable diagnostic information can be obtained. A history of previous ulcer may be elicited from the family or friends or from the patient. Evidence of emaciation may suggest the presence of cancer. Spider angiomas may lead to an immediate diagnosis of portal hypertension, with esophageal or gastric varices. The presence of jaundice may incriminate the liver. Light percussion may demonstrate splenic enlargement and lead to a similar conclusion. Inspection may reveal an abdominal mass necessitating an obvious diagnosis of cancer. Abdominal palpation must be done with caution, if at all, but may yield diagnostic information. A careful digital examination may reveal a tumor mass in the rectum, immediately indicating the diagnosis.

As soon as the danger of shock has been successfully met or it is apparent that major bleeding is not present, more intensive diagnostic measures can be instituted. These should be carried out in the following order: a searching history, a thorough physical examination, careful roentgenologic studies, — discussed and planned according to the findings of the history and physical examination, — endoscopy and a few laboratory tests. A meticulous history alone may indicate the segment to be studied even if a positive diagnosis cannot be made. Substernal epigastric symptoms imply upper-segment disease; periumbilical pain suggests the small intestine as the source of bleeding; discomfort in the right lower quadrant should lead to examination of the ileocecal region; and hypogastric distress suggests colonic disease. Positive physical findings may be diagnostic, but they are often notable for their absence. A palpable mass means cancer until proved otherwise by direct inspection. In most cases, the indicated roentgenologic studies, without manipulation, should be carried out within twenty-four to forty-eight hours of the occurrence of massive bleeding.

Gastroscopy, esophagoscopy and sigmoidoscopy should be postponed until active bleeding ceases. The indications for their use are clear. In the absence of definite roentgenologic findings, or when supplemental evidence regarding the nature of the bleeding lesion is desirable, endoscopic examination should be performed as soon after major bleeding has ceased as it can safely be done. Sigmoidoscopic examination should precede roentgenologic study. It may give more accurate information than a barium enema — in mild ulcerative colitis, for example. Similarly, it may reveal a polyp or a cancer that is difficult to demonstrate roentgenologically. In the presence of hemorrhoids or an anal fissure, sigmoidoscopy is essential to rule out a more serious source of bleeding at a higher level. With bleeding obviously arising from the lower digestive tract, a negative sigmoidoscopy immediately provides the proper impetus for a serious roentgenologic study of the upper colon and terminal ileum.

Gastroscopy, in experienced hands, is the only way to demonstrate an active gastritis that is responsible for upper-segment hemorrhage. Esophagoscopy is of use primarily in obtaining biopsy material from a suspected esophageal growth. It should not be used to visualize varices, which are almost always readily shown by proper roentgenologic studies.

Laboratory tests are of much less diagnostic importance than the measures discussed above in determining the source or nature of gastrointestinal bleeding. The finding of histamine achlorhydria in the presence of a demonstrated gastric lesion is of

value because it implies cancer as the underlying cause. Otherwise, gastric analysis is a needless procedure in the problem under discussion. When bleeding is due to a blood dyscrasia, such as thrombocytopenia, proper blood studies are obviously diagnostic. A prothrombin lack can be demonstrated only by a prothrombin determination, but decision regarding the underlying cause of blood loss is usually made by simple clinical observation, which is then confirmed by the appropriate laboratory test. In the main, laboratory findings are of aid only in demonstrating and measuring the effects of hemorrhage and in thus giving direction and timing to the proper treatment to correct blood loss.

The therapy of gastrointestinal hemorrhage is twofold. Immediate treatment has already been mentioned. It should be straighforward, adequate and continued until the pressing hazard of shock has been controlled, or until it is obvious that bleeding is not subsiding. In the latter event, a decision must be made for emergency surgical intervention. Subsequent therapeutic measures must be equally straightforward and directed toward obtaining medical control of the cause of bleeding or surgical removal of its source. When cancer is suspected or proved, radical surgical procedures must be instituted as soon as proper preoperative preparations to combat anemia, depletion, specific vitamin lack and the like have been carried out. In the presence of a proved peptic ulcer not requiring emergency surgery, simple feeding measures should be started early, and moderate sedation achieved. In my opinion, morphine should not be used because of its tendency to cause nausea and abnormal duodenal spasm; it is not a sedative, and barbiturates are more satisfactory. The current suggestion for the feeding of amino acid preparations may be useful in extremely malnourished patients, but simple, less distasteful feedings are usually preferable. Antacids may be helpful, and atropine may also be used to advantage either by mouth or parenterally. Iron should be avoided until all ulcer activity has ceased, because of its frequent irritating effect on the gastrointestinal tract. Transfusions, once the hemoglobin is at a safe level, are not needed and are probably inadvisable. After the bleeding episode has been successfully managed, proper elective surgery is usually indicated if the hemorrhage has been a major one. There are occasional exceptions to such a decision.

In bleeding from esophageal varices, feeding should be delayed because of the danger of further trauma to a ruptured varix. Because bleeding from this source is usually secondary to severe liver disease, transfusions or vitamin K or both are indicated for the additional purpose of correcting a bleeding tendency due to prothrombin lack.

Treatment of hemorrhage from gastritis is essentially the same as that from ulcer. If there has been prolonged vomiting, however, intravenous feeding must be utilized as a temporary expedient to replace fluid and electrolytes and to prevent gastric irritation. When massive bleeding occurs as a result of a local gastritis or an ulcer in a diaphragmatic hernia, medical treatment should usually be followed by elective transthoracic surgery aimed at repairing the hernia.

I shall mention only one other specific cause of bleeding — namely, ulcerative colitis. In this distressing condition, bleeding occasionally dominates the clinical picture. If intensive medical therapy does not control the blood loss in a reasonable and limited period, it is imperative that a decision be made for adequate surgical measures — ileostomy or colectomy, depending on which maneuver is indicated in the individual case.

Bleeding from direct trauma, which obviously falls into a separate category, is not considered.

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In this review of gastrointestinal bleeding as seen by the internist, I have tried to stress certain important points, none of which are new. Determination of the site and character of the hemorrhage — that is, exact diagnosis — is essential to proper, detailed therapeutic measures. Treatment must be directed toward immediate control of the sequelae of massive hemorrhage and subsequently toward adequate cure or management of the underlying cause. To achieve satisfactory results, the close cooperation of a well trained roentgenologist and of a competent surgeon is essential.

THE SURGICAL ASPECTS OF HEMORRHAGE FROM PEPTIC ULCER*

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A STUDY of the patients who have entered the surgical wards of the New York Hospital with serious hemorrhage from the gastrointestinal tract shows that the large majority were the victims of duodenal or gastric ulcer, whereas a minority presented a variety of other pathologic conditions. I was asked to discuss the large subject of hemorrhage from the gastrointestinal tract in its relation to surgery, but since it is obvious that I cannot cover so large a field in the short time at my disposal, I shall confine myself to the surgical aspects of hemorrhage from peptic ulcer, which, in my experience far overshadows in importance the others.

In reviewing this experience I find that of over 1800 patients with duodenal and gastric ulcer admitted to the surgical wards between September 1, 1932, and January 1, 1946, a total of 337 were admitted specifically because of serious hemorrhage. These cases have been reviewed from time to time. Holman,[1] in an analysis of the first 90 cases of serious hemorrhage, observed that 12 patients died, a mortality from hemorrhage of 13 per cent. In this group, 4 patients were in such a desperate condition that operation was never considered possible, 4 were operated on as a last resort, 4 recovered to a point where operation could have been performed but surgery was delayed, with the result that they died from a second massive hemorrhage. On the other hand, 4 patients operated on during active bleeding recovered. This experience shows that 8 patients in whom operation was not undertaken died from hemorrhage and that of 8 subjected to operation as a desperate venture, 4 recovered and 4 died — a surgical mortality of 50 per cent. Of the 74 patients who recovered from the primary hemorrhage under expectant treatment, 16 had been subjected to gastric resection at the time of the report and all had recovered.

Holman[2] subsequently studied 161 patients with severe hemorrhage admitted between 1932 and 1940, including the 90 referred to above. In this series there were 18 deaths during the period of active bleeding, a mortality from hemorrhage of 11 per cent. Thirteen patients died without having been subjected to surgery. Fourteen patients were operated on in the period of active bleeding, with 5 deaths — a surgical mortality of 35 per cent. Of the 134 patients who recovered from the primary hemorrhage under expectant treatment, 31 had been subjected to gastric resection at the time of the report, with 1 death — a mortality of 3 per cent.

Cliffton,[3] beginning where Holman left off, added 103 patients with serious hemorrhage admitted between July 1, 1940, and July 1, 1943. In this series there were 5 deaths during the period of active bleeding, a mortality from hemorrhage of less than 5 per cent. Three patients could not be brought into condition for operation and died two hours, eight hours and five days, respectively, after admission. Operation was performed in 8 cases during the period of active bleeding, with recovery in 6 and death in 2 — a surgical mortality of 25 per cent. Of the 92 patients who recovered from the primary hemorrhage, 41 had been subjected to gastric resection at the time of the report, with 2 deaths — a surgical mortality of 5 per cent.

Cooper,[4] in a study of 73 patients with serious hemorrhage admitted since Cliffton's report and covering the period from July 1, 1943, to January 1, 1946, found a total of 5 deaths, only 4 of which could be related to hemorrhage, however. This represents a mortality from hemorrhage of 5 per cent. Two patients died from hemorrhage without having been subjected to operation. Nine patients were operated on in the period of active bleeding — of whom 7 had gastric resections — with 2 deaths, a surgical mortality of 22 per cent. Of the 62 patients who recovered from the primary hemorrhage 33 were subjected to operation within four to six weeks, of whom 30 were subjected to gastric resection, 1 to a gastroenterostomy, 1 to a ligation of the gastric artery and 1 to an exploratory laparotomy. There was 1 postoperative death, an operative mortality of 3 per cent. As of January 1, 1946, there were 29 patients who had not been subjected to operation.

In summary, of 337 patients with peptic ulcer admitted to the hospital because of serious or massive hemorrhage, 27 (8 per cent) died from hemorrhage. Eighteen died without having been subjected to surgery, in the majority of cases the condition of the patient precluding, in the judgment of the surgeon, an operative procedure. Thirty-one patients were operated on in the period of active primary hemorrhage, with 9 postoperative deaths — a surgical mortality of 29 per cent. From the location of the ulcer and the source of bleeding it is probable that all 31 patients would have died had surgery not been undertaken. It thus appears that 49, or 15 per cent, of the total number of patients admitted because of severe hemorrhage were examples of fatal hemorrhage, a higher percentage than is usually appreciated.

Of the 288 patients who recovered from hemorrhage under expectant treatment, 105 were sub-

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jected to operation at the time of the reports mentioned above. The operation was, with few exceptions, a gastric resection with removal of the ulcer — and was performed usually within four to six weeks after the primary hemorrhage. There were 4 postoperative deaths, a case mortality of 4 per cent. The remaining 183 patients were discharged from the hospital to be followed in the clinic.

From the 18 patients who died without operation, in whom permission for autopsy was obtained in a high percentage of cases, from the 31 subjected to operation during the period of active bleeding and from the 105 patients operated on within four to six weeks after recovery from the hemorrhage that led to admission, a total of 154 cases, it has been learned that the location of the ulcer with reference to immediately adjacent large arteries is the determining factor in the seriousness of or fatality from hemorrhage. Without exception the duodenal ulcers with hemorrhage that was fatal or unchecked by a conservative regimen were located on the posterior duodenal wall and had eroded the pancreaticoduodenal artery or one of its major branches; if gastric, the ulcers were on the lesser curvature, eroding a large branch of the right or left gastric artery. The pathologic picture was strikingly similar in all cases: the ulcer was deep and presented a hard, fibrous base in which there was an eroded, open artery whose lumen, in some of the specimens at autopsy, was large enough to admit a matchstick. In this series the ulcer that gave rise to fatal hemorrhage, if unchecked by surgery, was located in one or the other of the two areas indicated and was usually chronic, and the hemorrhage was arterial and more frequently from a single eroded artery.

At operation performed during the period of bleeding, a conical clot temporarily stopped the bleeding from even a large eroded artery, but I have also observed how easily such a clot may be dislodged and how unlikely it is to become organized and fixed. It is not implied from these statements that hemorrhage from ulcers of the posterior wall of the duodenum or lesser curvature may not, under a medical regimen, spontaneously cease, for it is of course the size of the blood vessel eroded that is the determining factor. The ulcers with hemorrhage that was checked under a conservative regimen were in most cases located away from the two dangerous vascular areas described above or, if located in those areas, had not eroded a large artery. It is the early, acute and not deeply penetrating ulcers — those of the anterior wall of the duodenum and those of the distal portion of the lesser curvature and fundus of the stomach — that give rise to less dangerous hemorrhages.

It is evident from this experience that in any series of patients with serious hemorrhage as the primary cause of admission to the hospital, there will be two groups — a minority, in whom hemorrhage, if not surgically checked, is fatal, and a majority, in whom hemorrhage, under expectant treatment, spontaneously ceases. In our experience the former group varied in different periods from 18 to 11 per cent of the total, averaging about 15 per cent. No doubt this percentage varies in different clinics, but it is evident from the literature that surgical clinics quite generally have a minority group of greater or lesser size to contend with.

The immediate clinical problem is accurately to differentiate the group whose hemorrhage is uncontrollable short of surgical measures and that whose hemorrhage ceases under conservative measures. The immediate surgical problem is how, in patients with uncontrollable hemorrhage, to arrange all details of a surgical procedure so as to save the greatest number of lives. A third, but not so immediate problem, is how most intelligently to care for the majority group, who have recovered from hemorrhage under expectant treatment.

The differentiation of patients whose hemorrhage is likely to prove fatal if unchecked by surgery and those in whom it ceases under a proper conservative regimen has proved extremely difficult. Patients are admitted in all stages of reaction to hemorrhage. Some are in such a desperate condition that they die in the emergency unit before they can be transferred to the wards, in spite of large or repeated small blood transfusions. Others less profoundly affected show great variations in their reactions to hemorrhage, as manifested by physical appearance, pulse rate, respiration, blood pressure, sweating, mental state, blood counts and hemoglobin determinations. It is well known that patients react differently to the loss of blood and that unless some accurate data can be obtained regarding the amount of blood vomited or passed by rectum, it may not be known on admission of the patient how large a hemorrhage has taken place. Moreover, the clinical picture presented cannot immediately reveal whether the hemorrhage is derived from an eroded pancreaticoduodenal artery and will continue, proving fatal if unchecked, or whether it is derived from an ulcer in a less dangerous location and will cease under a conservative regimen. It is a question whether one should attempt, in the early period of observation, to establish the location of the ulcer and thus clarify the situation regarding therapy. In many patients, attempts at gastroscopy are unwise and impossible; a swallow or two of barium, with observation under the fluoroscope, had tragic consequences in 3 cases, being promptly followed by a fatal secondary hemorrhage. It appears logical, in all the circumstances, to attempt to differentiate patients whose hemorrhage is likely to prove fatal and those whose hemorrhage is likely to cease spontaneously by following the early clinical course under appropriate treatment — that is, to put them to bed, to administer moderate doses of morphine to induce quiet, to withhold food

and fluids by mouth, to supply fluids by vein and to give adequate blood transfusions.

If such a practice is followed, the response to these measures falls into two main groups: some patients merely hold their own and do not improve or they continue to fail, for they are still bleeding and the blood escapes from the open artery in the base of the ulcer as rapidly as or more rapidly than it is introduced into the veins; others improve, as evidenced by physical appearance, pulse, blood pressure and other favorable signs. With the latter, it may be assumed that the hemorrhage had ceased at the time of admission or, if continuing, has greatly decreased. The fact that these patients improve is not positive proof that the hemorrhage was not derived from an open pancreaticoduodenal or major branch of the right or left gastric artery, for under a strict regimen, as indicated above, some patients suffer a second massive or even fatal hemorrhage in the first two hospital weeks; this may occur spontaneously or may be initiated by the administration of food or a swallow of barium with the purpose of localizing the lesion. Of all the criteria assembled to differentiate the cases of hemorrhage that are likely to prove fatal, the failure of hemorrhage to stop under a strict medical regimen and the recurrence of hemorrhage after it has temporarily stopped and while the patient is on a strict medical regimen are the most positive. In all cases that exhibited these manifestations the ulcer was located on the posterior wall of the duodenum, implicating the pancreaticoduodenal artery, or on the lesser curvature of the stomach, involving a large branch of the gastric artery. In passing I may say that these statements also apply to patients admitted not because of hemorrhage but because of other symptoms of ulcer who, while under a strict medical regimen, have a serious hemorrhage.

It therefore appears that among patients admitted because of serious hemorrhage there will be some — in the experience cited above, 15 per cent of the total — who die of hemorrhage that is not surgically checked. The most positive indications of such hemorrhage are: the failure of improvement under a strict medical regimen, including adequate blood transfusions, with or without evidence of continuing bleeding, such as the vomiting of blood and the passage of blood by rectum, and the recurrence of hemorrhage under a strict medical regimen. Patients who present these indications must seriously be considered subjects for early operation, for otherwise a high percentage will die.

Other factors affect the seriousness of hemorrhage in ulcer. Age has been shown to be a factor by a number of authors, and the experience discussed above supports the view that hemorrhage is likelier to be serious and fatal in patients over fifty years of age. This is due not only to the higher incidence of arteriosclerosis but also to cardiorenal complications. Sex is also a factor, and it is well known that fatal hemorrhage is less frequent in women than in men.

Thus far in my discussion I have tried to define and segregate patients with serious or massive hemorrhage in whom immediate or early operation must seriously be considered. What are the criteria in arriving at a prompt decision to operate? I have referred to patients who are admitted in profound shock and, judged by the usual criteria, present every contraindication to operation. Should operation be delayed, in the hope that the patient will improve and be less grave a surgical risk, or should contraindications be disregarded and a desperate surgical venture undertaken? Both methods of approach to the problem have been tried. Whether operation is performed early or delayed, a fairly high mortality can be expected. The question is, Which will achieve the lower mortality? From this admittedly limited experience, early operation appears to be the better choice. The principle — established in wounds of war and accidents of civil life — that active hemorrhage must be controlled before progress can be made toward saving life is equally applicable in the type of hemorrhage under discussion. In exposing an ulcer of the posterior duodenal wall with an eroded, actively bleeding, pancreaticoduodenal artery, I have not only been amazed at the amount of blood that can be poured into the duodenum in a short time but also struck with the futility of blood transfusions as a means of saving life until the bleeding vessel has been controlled.

The question of when to operate in this particular group of cases has been discussed by a number of authors, and it appears that early operation — within twenty-four to forty-eight hours after the onset of hemorrhage — will save more lives. Finsterer,[5] an advocate of operation for massive hemorrhage in chronic ulcer, reports that in 59 patients operated on immediately or within forty-eight hours the mortality was 5 per cent, whereas in 53 operated on late it was over 30 per cent. Gordon-Taylor,[6] Oliani[7] and others also found that early operation gave better results. The experience in this hospital shows that of 21 patients operated on early, 2 died — a mortality of 10 per cent — and that of 10 operated on late, 7 died — a mortality of 70 per cent. The experience quoted indicates that operation should be promptly decided on and executed.

After operation has been decided on, one of the most important factors in a successful outcome is an unlimited amount of blood available for transfusion. The introduction of blood, previously begun in the ward, should be continued throughout the operation and after operation, according to indications. The treatment of the wounded in war demonstrated the value of large amounts of whole blood in patients with massive and continuing hemorrhage, and the situation in hemorrhage from ulcer is similar. The primary object of surgery is to con-

trol hemorrhage and save life; the treatment of the ulcer from an immediate viewpoint is secondary, as it is in acute perforation. The operative procedure of choice, then, should be the quickest and simplest that will completely control hemorrhage.

For both duodenal and gastric ulcers, the operations performed include the following: the local ligation of the artery in the base of the ulcer by an encircling ligature; the ligation of the artery or arteries outside the visceral wall; the local excision of the ulcer with the control of hemorrhage, with such additional procedures as may be necessary to re-establish the continuity of the gastrointestinal tract; and gastric resection, including the bleeding ulcer. Experience with these procedures shows that they all have some disadvantages. Local ligation of the bleeding vessel in the base of the ulcer and the ligation of vessels outside the visceral wall have not proved uniformly successful. A continuation of the ulcerative process or the cutting through of ligatures or their combination may result in a recurrence of hemorrhage during the first or second week after operation. In ulcers high on the lesser curvature of the stomach, experience with these two procedures has been particularly unfavorable. Because the lesions were so high as to encroach on the esophagus, neither local excision nor any other procedure appeared feasible. In 3 patients with lesions of this sort, hemorrhage was temporarily checked but recurred and resulted in death. Post-mortem examination showed further erosion and reopening of the blood vessels. Local excision of the ulcer with the control of hemorrhage is definitely a safer procedure from the viewpoint of permanently controlling hemorrhage. In lesions favorably situated, it can be done almost as rapidly as the preceding two procedures. In lesions of the stomach and duodenum adjacent to the pylorus, the excision of the ulcer and the necessary repair may occlude the stomach or duodenum and make necessary an additional procedure, such as a pyloroplasty or a gastroenterostomy, which prolongs operation and adds to its hazards in a depleted patient. Gastric resection with removal of the ulcer is the most formidable operation for dealing with the situation. Its duration and often its technical difficulties are disadvantages. If it succeeds, there is in addition to saving life the greater probability of curing the patient of the disease.

These are the most frequent methods of surgical treatment of the bleeding ulcer. It is apparent that rules for their use cannot be stated. The judgment of the surgeon must guide him in determining which procedure he will use in an individual case. Generally speaking, however, it can be said that local attempts at controlling hemorrhage without removal of the ulcer are the least safe of the methods of permanently controlling hemorrhage.

As I have indicated above, approximately 15 per cent of patients who enter the hospital with massive hemorrhage die unless they can be saved by prompt surgery. Eighty-five per cent, under a careful medical regimen, including blood transfusions, recover from the hemorrhage for which they are admitted. What should the policy toward this group of patients be? As pointed out above, of 288 patients who recovered from their primary hemorrhage, 105 were subjected to operation — the large majority, to gastric resection — within four to six weeks after the primary admission for hemorrhage. There were 4 postoperative deaths, a mortality of 4 per cent. One hundred and eighty-three patients had not been operated on at the time the various studies were made but had been discharged from the hospital to be followed in the clinic.

I had hoped to be able to report the follow-up studies on the entire series of cases, but I could not complete the task in time for this meeting. I am, however, able to report on the group of 73 cases occurring between July 1, 1943, and January 1, 1946, in which 2 patients died without operation, 9 were operated on during the period of active hemorrhage, with 7 recoveries and 2 postoperative deaths, 33 were subjected to operation within four to six weeks after recovery from the hemorrhage for which they were admitted and 29 were not subjected to operation but were discharged to be followed in the clinic.

Of the 7 survivors among the 9 patients subjected to operation during the period of active hemorrhage all were subjected to gastric resection, with satisfactory results from the primary resection in 6. One had a poor result but was subjected to a second resection with a satisfactory result. The results were therefore satisfactory in this group.

Of the 33 patients subjected to operation within four to six weeks after recovery from the primary hemorrhage, 25 had primary gastric resections, 5 had secondary resections (these patients had previously been operated on); 1 had a gastroenterostomy, 1 had a ligation of the left gastric artery, and 1 had an exploratory laparotomy.

Of the 25 patients with primary resections, 1 died after operation. Of the 24 survivors, 21 at present have satisfactory results and 3 have poor results; the 3 patients with poor results have developed recurrent ulceration, with recurrent hemorrhage, but all are living at the present time.

Of the 5 patients with secondary gastric resections, 3 have satisfactory results at present. The 2 with poor results developed recurrent ulceration with hemorrhages — both were subjected to further gastric resections and both still have poor results, with recurrent hemorrhages, but are alive.

The patient subjected to gastroenterostomy has at the present time a satisfactory result. The patient subjected to ligation of the left gastric artery had a poor result, with recurrent hemorrhages. He was subjected to a gastric resection during active bleeding, with a satisfactory result at present. The patient

subjected to exploratory laparotomy without the discovery of a demonstrable active ulcer has a poor result, with recurring hemorrhages. He is living at the present time.

In summarizing this group of 33 patients it appears that they have been subjected to thirty-five operations (thirty-three gastric resections) in attempts to control hemorrhage and to prevent recurrent ulceration. There was 1 postoperative death — an operative and case mortality of 3 per cent. Of the survivors, 26 (81 per cent) have satisfactory results at present and 6 (19 per cent) have poor results with recurring hemorrhages. Gastric resection, in this group, was effective in controlling hemorrhage and preventing recurrent ulceration in 84 per cent of the cases.

Of the 29 patients discharged from the hospital without having been subjected to operation, 28 have been successfully followed. Of these, 24 have a satisfactory result from the viewpoints of both absence of recurrent hemorrhage and relief from other ulcer symptoms. Four with poor results have had recurrent hemorrhages but are living. Under a careful medical regimen, therefore, the results were satisfactory in 85 per cent of these patients.

I am unwilling to draw any definite conclusions from these data. The follow-up period is too short, for the majority of patients have been followed less than three years. From all the studies on ulcer that I have made it is evident that accurate statements regarding the effectiveness of either medical or surgical measures cannot be made on the basis of a follow-up period of less than five years, and I must add that statements based on such a follow-up period must be modified in the years that follow. Again, the data that I have presented cover only a part of the entire series, a complete study of which may show results at variance with those given. From such data as I have on the entire series, it appears that 37 per cent of these patients were subjected to early gastric resection (within four to six weeks) and that 63 per cent were treated medically. From observations admittedly incomplete I find that gastric resection, after a relatively short follow-up period, assures control of hemorrhage and prevention of recurrent ulceration in 84 per cent of cases, with a primary surgical mortality of 3 per cent. I find, also, that on the basis of a similar short follow-up period, a medical regimen may yield highly satisfactory results in selected cases. I have no positive evidence that every patient who bleeds must necessarily be subjected to surgery. But there is evidence that a certain percentage of cases should be subjected to early surgery. First, it is known that hemorrhage, with the exception of acute perforation, is the most frequent cause of death in ulcer. Secondly, it is known that although acute ulcers may give rise to serious hemorrhage, the deeply penetrating, more chronic ulcers oftener cause dangerous and fatal hemorrhage — perhaps I should use the term "actively penetrating" rather than "chronic ulcer," for Holman et al.[8] found that in older patients the increased mortality from hemorrhage does not bear a relation to the age of the ulcer, since the average duration of symptoms was slightly over four years in those who recovered from hemorrhage and four years in those who died. Thirdly, age, in the experience discussed above and in that of a number of authors, is a factor, more patients forty-five to fifty years of age and over being likely to suffer hemorrhages leading to death than patients in younger age groups. The higher death rate in the older age groups is not wholly due to the hemorrhage but in part to a higher incidence of complications caused by loss of blood, particularly cardiorenal complications. Again, the repetition of hemorrhage is believed by some to be of importance in determining treatment. Jordan and Kiefer,[9] for example, found that 70 per cent of patients who had two or more hemorrhages suffered further hemorrhages. And finally, Holman[10] and others have noted that patients with chronic ulcer and with a history of present or past hemorrhage do not do well under a medical regimen and are prone not only to a continuation of pain and other symptoms but also to recurrent hemorrhage. This finding is not supported by the follow-up studies in the small group of 28 cases considered above, who were not followed for a sufficiently long period of time, however.

Although these observations have a bearing on the problem of treating patients who have recovered from the hemorrhage that brought them to the hospital, it must be admitted that they are somewhat vague to be formulated into a clear-cut policy. Any policy for this group of patients cannot well be determined on the basis of hemorrhage alone; it must include consideration of the ulcer and its duration, location, pathologic characteristics and probable tendency to heal. If a patient has suffered a serious hemorrhage and harbors an ulcer that experience indicates is unlikely to respond to a medical regimen, the occurrence of hemorrhage is an added reason for surgical therapy; if experience suggests that the patient has an ulcer that is likely to respond to a medical regimen, a first or second hemorrhage should not weigh too heavily in the decision to recommend early surgery. Until more clear-cut information is available, the decision regarding therapy in this group of cases must rest on the consideration of all the factors enumerated. If surgery is decided on, gastric resection, with invariable removal of the ulcer if possible, is the operation of choice, although it does not necessarily protect the patient against either subsequent ulceration or hemorrhage.

This discussion has been confined to hemorrhage in patients with peptic ulcer. I should, perhaps, refer to a related group of patients who have massive and sometimes fatal hemorrhage but who fail to present a demonstrable ulcer. This group of patients has

been a particularly discouraging one. Pathologically, the information regarding the source or sources of hemorrhage has been meager. At autopsy the pathologist has, generally speaking, failed to find an ulcer or other causes of hemorrhage. In one case the pathologist did not find even an erosion of the mucosa of the stomach and duodenum, but when the gastric artery was connected with a pressure bottle of salt solution a jet of fluid was projected from the mucosa. The area was excised, and serial sections showed a small ruptured aneurysm covered by intact mucosa. At operation in these cases the most careful inspection and palpation of the stomach and duodenum fails to demonstrate an ulcer. In some of these cases the stomach has been opened by a long incision parallel with the greater curvature, the stomach literally turned "inside out" and the entire mucosa not only of the stomach but also of the proximal duodenum carefully examined, without the demonstration of an ulcer. In the majority of cases so examined the bleeding temporarily ceased and a source of hemorrhage was not found. Yet within a week the patient may suffer another devastating hemorrhage.

Clinically patients suffering from this type of hemorrhage often fail to present any symptoms that serve to differentiate them from those with ulcer, although a clear-cut history of ulcer may be absent. The first hemorrhage may be fatal, and the assumption is that the patient has bled from an ulcer until autopsy proves otherwise. Again, patients may have repeated hemorrhages from which they recover under appropriate treatment. A patient of one of my associates whom I saw in consultation had fifty-eight massive hemorrhages over a period of twenty-five years and had been admitted to and carefully studied in many of the important clinics throughout the country. He had been operated on in one clinic and a gastric resection performed even though an ulcer was not demonstrated. He entered the New York Hospital exsanguinated from his fifty-ninth hemorrhage. He recovered and was again operated on because of the suspicion of a duodenal ulcer. A further segment of duodenum was resected, but an ulcer was not found. After having shown such a tenacity of life for so many years, it seems a pity that the patient recently got into a fight, was knocked to the pavement and died of an intracranial hemorrhage.

So far as diagnosis and treatment are concerned, it appears to me that these cases must be classified with those of hemorrhage from ulcer. The absence of a history of ulcer is scarcely of sufficient weight for operation to be withheld in the presence of a hemorrhage immediately threatening life, and should recovery occur under expectant treatment, further studies may be helpful in determining treatment. Such a program will result occasionally in the embarrassment of the surgeon who at operation fails to find an ulcer or other source of hemorrhage. What he is to do under these circumstances I leave to his best judgment.

Summary

A study of 337 patients admitted to the hospital because of massive hemorrhage due to peptic ulcer is presented. Of these patients 27 (8 per cent) died from hemorrhage — 18 without having been subjected to operation and 9 following operations performed on 31 patients during active bleeding.

In the experience on the surgical ward service of the New York Hospital 49 (15 per cent) of all patients admitted with massive hemorrhage presented a fatal type of hemorrhage and in all probability would have died without the intervention of surgery.

Two hundred and eighty-eight patients (86 per cent) admitted because of hemorrhage recovered without immediate or early surgical intervention.

In patients with the fatal type of hemorrhage the location of the ulcer, if duodenal, is on the posterior duodenal wall and, if gastric, on the lesser curvature. The blood vessels causing the hemorrhage are the pancreaticoduodenal and the right and left gastric arteries or their major branches.

In an attempt to differentiate patients with fatal and nonfatal types of hemorrhage the most consistent criteria are failure to improve promptly under a strict regimen of bed rest, moderate doses of morphine, withholding fluids and food by mouth and adequate blood transfusions and the recurrence of hemorrhage while the patient is on a strict regimen.

If operation to save life is decided on it should be done within twenty-four or forty-eight hours of the onset of hemorrhage. The mortality in patients operated on early was 10 per cent, whereas that in patients operated on late (after forty-eight hours) was 70 per cent.

Large amounts of blood administered as transfusions before, during and after operation are of great value in operations performed for the control of hemorrhage.

Local ligation of the vessels giving rise to hemorrhage has not consistently and permanently controlled hemorrhage. Local excision of the bleeding ulcer and gastric resection, including removal of the ulcer, have given the best results.

In patients who recover from hemorrhage on a strict medical regimen the question of recommending surgery or of continuing a medical regimen is vital. No definite criteria for differentiating those who should be subjected to surgery and those who may properly be continued on a medical regimen have been developed. On the other hand, age over fifty, the occurrence of repeated hemorrhages, the chronicity and unfavorable location of the ulcer and failure in the past to respond to a medical regimen are factors suggesting surgery.

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ROENTGENOLOGIC EXAMINATION IN PATIENTS WITH BLEEDING FROM THE GASTROINTESTINAL TRACT

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MASSIVE hemorrhage from the gastrointestinal tract, particularly hematemesis, is one of the dramatic events in medicine that deeply impress both patient and physician. The question that presents itself urgently to both is, What is the cause of the bleeding? At times the history may give a clue to the diagnosis, whereas at others the bleeding takes place without any preceding symptoms or signs. In rare cases a blood dyscrasia, usually easily recognized, has prompted the hemorrhage, but the answer to the question usually depends on the demonstration of an anatomic lesion.

The roentgenologist is burdened with the responsibility of finding the source of bleeding in a patient who is often sick and difficult to examine. The plan of action which should be agreed on after thoughtful discussion by both the roentgenologist and the physician in charge of the patient, varies somewhat from case to case. If there is no clinical hint regarding the location of the point of bleeding — that is, whether it is in the upper or the lower part of the gastrointestinal tract — a scout film of the abdomen and examination of the large intestine should precede that of the esophagus, stomach and duodenum. A careful study of the small intestine forms the last part of the examination. Usually, however, the type of hemorrhage indicates roughly which part of the gastrointestinal tract is the source of bleeding, and the suspected region should be examined first. Massive hemorrhage in the majority of cases arises in the upper part of the digestive tract, and the question to be decided first is when the patient can best and safely be submitted to barium-meal studies.

In the past the tendency was to delay such examination for two or more weeks, since it was thought that one at an earlier date not only endangered the patient but also, because of his precarious condition, furnished somewhat unreliable results. In recent years this attitude has changed, and the manifold advantages of early roentgenologic examination are recognized.

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A patient may bleed from a gastric cancer, in which case delay of examination would mean delay in operation and, in turn, delay in removal of the malignant source of bleeding. Bleeding ulcers in people over fifty years of age have been shown to have a mortality higher than that in younger persons. The necessity of careful appraisal of these patients in whom early operation is preferable has been emphasized by Allen.[1] Should the necessity for surgical intervention arise, the operation is connected with greater risk unless the diagnosis has been established preoperatively. If the patient is bleeding from an ulcer, it is of advantage to the surgeon to know where the ulcer is — whether in the stomach or in the duodenum, and whether on the anterior or the posterior wall. The bleeding lesion may not be in the abdomen but higher in the gastrointestinal tract. A number of patients with esophageal varices have, in a search for the source of bleeding, been subjected to negative abdominal explorations. There is another reason in favor of early examination: a bleeding ulcer may heal within a short time, and examination at a later date may leave physician and patient with the uncomfortable mystery of unexplained hemorrhage.

In recent years the dietary regime of the bleeding patient has become more liberal, food being administered in the early days of hemorrhage. There is no reason to assume that a watery suspension of barium sulfate is more dangerous than food. In all probability it is even less so, because it does not stimulate peristalsis and secretion to the same degree that food does. For some time, following the example of Hampton,[2] I have not hesitated to examine a patient shortly after bleeding has stopped, or even during bleeding, although I do not examine patients in shock. The examination, without any palpation, is made with the patient in the horizontal position, peristalsis and gravity (turning him from side to side) being used as the means of distributing the barium over the inner surface of the esophagus, stomach and duodenum. So-called "spot films" — that is, films taken during fluoroscopy at the optimal moment of

filling and projection — are taken whenever they are deemed advisable and are of great help.

* * *

It may be worth while to describe the routine procedure in the roentgenologic examination of the upper gastrointestinal tract in a patient who has had a recent hemorrhage. He is placed in the supine position, rotated slightly to the left. A swallow of barium is followed through the esophagus fluoroscopically, and the presence of large varices may be detected. Further examination of the esophagus is postponed until the end of the examination, to prevent overfilling of the stomach at this stage. An additional two or three swallows are usually needed to outline the posterior part of the fundus of the stomach. Complete filling of the fundus is not obtained at this point, since it necessitates too much barium. The patient is then rotated to the right side until a point has been reached where the barium leaves the fundus and falls slowly through the body toward the antrum. More barium is given, and the stomach is observed until most of that from the fundus has emptied into the lower portion of the stomach. In this position the lesser curvature forms the dependent portion of the stomach, and ulcers may be seen clearly, face on, through the air that fills the greater portion of the body of the stomach. The significance of this position cannot be overemphasized.

The patient is then returned to the supine position and rotated slowly to the left side. This maneuver tends to produce reasonably complete filling of the upper half of the stomach. If the turning of the patient is continued until he is on his face, incomplete air demonstration of the fundus and massive filling of the lower half of the stomach result. The examination of the esophagus in both oblique diameters is completed while the patient is lying on his stomach. The examination of the duodenal cap has been described in detail by Hampton.[2] The outline of the cap is usually seen while the patient is in the face-down position. Better demonstration of the shape and of the relief of the cap is obtained, however, in the last phase of the examination: the patient is turned on his right side, the cap being allowed to fill with barium, after which he is returned to the supine position and to his left side. This permits the air in the stomach to reach the cap and produce an air-and-barium contrast picture of the cap (Hampton's maneuver). In the same position the antrum and second portion of the duodenum may be demonstrated with contrast filling.

Complete rotation of the patient is not always necessary, since the source of bleeding may be discovered after the first few swallows of barium or a single spot film may be sufficient for its demonstration, when the patient may return to the ward. In the patient with active hemorrhage for whom the prone position is thought to be inadvisable for clinical reasons, this part of the examination may be omitted and the patient studied only on his back and on his side; this omission will reduce somewhat the completeness of the examination.

The early examination, as described above, is adequate for study of the esophagus and satisfactory for examination of the duodenum, but it does not always demonstrate the entire stomach. The only real danger involved is in the transport of a patient bleeding from the gastrointestinal tract. I consider this danger negligible if a sudden increase in intra-abdominal pressure is prevented, and this can be avoided by lifting the patient on the bed sheet from the stretcher to the examining table and back again.

Good clinical judgment and common sense are essential in the selection of bleeding patients for early examination. Obviously a patient should not be examined during clinical shock. It is usually unnecessary to examine one while he is actively bleeding. Blood clots that lie in the stomach handicap the proper interpretation of the roentgenograms, although they do not prevent diagnosis of varices of the esophagus, large ulcers of the stomach or ulcers of the duodenum. It appears reasonable to wait at least twenty-four or forty-eight hours after an acute, massive hemorrhage. Earlier examination may be necessary if the patient has had previous gastrointestinal bleeding whose cause was not found, or if he shows evidence of continued arterial bleeding calling for immediate surgery. Such cases are the exception, however, and in general it is wise to postpone examination until the active, massive bleeding has subsided. If the source of hemorrhage is known from a previous examination, re-examination may be delayed until the patient's condition permits study in the upright as well as in the horizontal position. It would be useless, for example, to submit the patient and the roentgenologist to the difficulties of early examination in a case of known duodenal ulcer admitted to the hospital because of a fifth bleeding episode.

Any patient in whom early examination has not demonstrated the cause of hemorrhage should be re-examined at a later date when palpation is possible and he is permitted to stand. Some bleeding lesions are better demonstrated during the early examination, and others at the later, more convenient and more thorough one. In spite of every diagnostic maneuver known to the roentgenologist, the source of bleeding in a certain number of cases will remain obscure.

* * *

The lesions that produce hemorrhage from the gastrointestinal tract are manifold. It is impossible

to discuss them all, but a few are selected to show some of the problems with which the roentgenologist is confronted.

By far the most frequent cause of bleeding is a duodenal ulcer, and good demonstration of the duodenal cap is one of the important factors in the examination. Hampton's maneuver, described above, is indispensable for this purpose, since most bleeding ulcers arise from the posterior wall and are particularly well demonstrated in this position. A normal-appearing cap does not rule out bleeding from a duodenal ulcer, since the ulcer may lie distal to the cap. Another diagnostic error may be caused by a large ulcer that replaces the entire area normally occupied by the duodenal cap and thus simulates a normal cap.

Gastric ulcers, particularly if they are not large, may disappear with unexpected speed; I have seen bleeding ulcers disappear within two weeks. As mentioned above, routine roentgenograms taken in the horizontal position may miss ulcers, particularly those high on the lesser curvature and posterior wall. Spot films, taken with the patient face up and turned on the right side, show the crater through the air of the stomach. If the ulcer lies on the posterior wall, it may be clearly seen in profile in this position.

If the bleeding is from cancer, and the cancer is large, fluoroscopy and a single spot film may be sufficient to demonstrate it. Blood clots, however, may produce a picture similar to polypoid tumor and in questionable cases should be excluded by re-examination. It should be borne in mind that a blood clot may remain unchanged in the stomach for some time, particularly if the patient has anacidity.

One of the great advantages of early examination is the possibility of diagnosing, and to a certain extent excluding, varices of the esophagus. If varices are demonstrated, in all probability the source of bleeding has been found. Varices may be present in the absence of splenomegaly, ascites and palpable liver anomalies, and hemorrhage may be the only clinical symptom. On the other hand, not every patient with demonstrable varices bleeds. The recognition of varices is difficult at times. The esophagus, if filled with enough barium, may appear practically normal except for a slight widening, or peristalsis may empty the dilated vessels, producing a normal appearance. Even when extensive varices are present, only the relief picture may reveal the vascular phenomena. The relief picture represents the barium coating of the esophagus after the main bolus has passed through it. Varices occasionally extend into the stomach, and their appearance suggests a tumor in the fundus; in rare cases they are confined to the stomach. Under these circumstances, their diagnosis is extremely difficult.

Gastritis, particularly if many erosions are present, may cause marked hemorrhage. The roentgenologic diagnosis of gastritis is difficult and is possible in only a small number of cases. The erosive form, in which bleeding is most frequent, is rarely demonstrable, but if it is, the characteristic appearance is one of multiple shallow craters surrounded by a halo of edema. In acute alcoholic gastritis, which often causes hemorrhage, one sees evidence of marked hypersecretion with some swelling of the folds. At times this swelling produces a tumorlike appearance, but it usually disappears within a few days. On the other hand, in gastritis, the stomach may appear completely normal roentgenologically, and only by gastroscopy may the diagnosis be made.

Hemorrhage from a hiatus hernia is easily understood if a large crater is seen in the ring of the hernia, but bleeding occasionally occurs without ulcer. I have seen cases in which at autopsy nothing was found to explain the patient's hemorrhage except erosive gastritis, particularly in the herniated portion of the stomach.

Repeated hemorrhage without other clinical symptoms is often found in tumors that arise beneath the mucosa of the stomach wall — the so-called "spindle-cell tumors," which include leiomyomas, fibromas, neurofibromas and their malignant variants. Their roentgenologic appearance is similar and characteristic.

Examination of a bleeding patient should not be stopped at the duodenal cap. Tumors of the duodenum are rarer than those of the stomach, but every roentgenologist of experience has seen a fair number of them. They are frequently missed unless they are carefully looked for. Demonstration of a possible source of bleeding should not prevent one from continuing the examination to its completion unless the patient is in a precarious condition, since at times another bleeding lesion is found. I have seen, for instance, a bleeding fibrosarcoma of the third portion of the duodenum in a patient with a large duodenal crater that at first had seemed to explain the hemorrhage.

Only a few examples have been selected to demonstrate the problem with which the roentgenologist is confronted in dealing with a bleeding patient. A large number of other lesions, especially those in the small intestine and colon, have been omitted from this discussion.

Summary

The roentgenologist plays an important role in the handling of a patient bleeding from the gastrointestinal tract. In most cases he is burdened with the responsibility of demonstrating the anatomic lesion that has caused the hemorrhage, and to do so it may be necessary to examine every portion of the gastrointestinal tract.

The routine roentgenologic examination of the upper gastrointestinal tract in a bleeding patient is described.

Indications and contraindications for roentgenologic examination soon after, or during, hemorrhage are discussed.

In spite of the most careful examination, the cause of bleeding may remain roentgenologically obscure.

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AN OUTBREAK OF INFLUENZA A IN A BOYS' SCHOOL*

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FOLLOWING the Christmas vacation of 1945–1946, there were admitted to the infirmary of a boys' school of about 680 boarding students, located thirty miles north of Boston, several boys with "colds" characterized by enough malaise so that the patients willingly sought medical advice. After hospitalization of the first patient 30 patients were admitted for upper respiratory infections during the next ten days, 138 more during the second ten-day period and 46 more during the third ten days. The outbreak then subsided. The epidemiologic data are presented graphically in Figure 1.

Clinical Aspects

These illnesses of the respiratory tract were diagnosed clinically as common cold in 87 cases, influenza in 97, acute pharyngitis in 14, otitis media in 11, hemolytic streptococcus pharyngitis in 3 and primary atypical pneumonia of unknown etiology in 3.

Detailed questioning of 50 patients selected at random disclosed that the onset of symptoms was gradual in 46 and abrupt in 54 per cent. Constitutional symptoms included malaise in all cases, headache in 68 per cent, chilliness in 44 per cent and muscle aches in 26 per cent. Cough was noted in all cases, coryza and a sore or "scratchy" throat in 68 per cent and earache in 32 per cent.

In about 80 per cent of the cases the first symptom was one referable to the upper respiratory tract, such as a sore or "scratchy" throat, "stuffiness," "sniffles" or a "cold" or cough. In the remaining 20 per cent the first symptom was malaise or prostration.

The symptom of malaise is more difficult to define than it is to experience. The statement that malaise was present in all cases means that all the 50 patients questioned minutely felt "lousy" at approximately the time they sought hospitalization. This word usually chosen by the patient, although of doubtful elegance, has the merit of being unmistakable in its connotation of lack of well being. A more accurate picture of the systemic symptoms is afforded by the fact that whereas all the boys interrogated had at least transient malaise, only 21 per cent of the whole group had abnormal fatigue and weakness — that is, prostration — as evidenced by remarks made on the infirmary records.

Likewise the fact that all those closely questioned had cough needs some qualification. In many cases the reply to the question, "Did you have a cough at any time?" was, "Well, not enough to speak about." Further interrogation, however, elicited the information that such a patient had a slight "hack" or a "scratchy cough." Cough was thus present to a greater or less degree in each member of this group but was noticeable enough to be recorded in the infirmary records in only 20 per cent of the total number of patients.

Physical and Laboratory Findings

As one might suspect, objective signs were scant except for injection of the mucous membranes of the nasopharynx or the tympanum and for a variable amount of coryzal discharge.

The average temperature was 101°F. at the height of the illnesses, — usually at or shortly after admission, — the range being between 98 and 104°F. There was nothing distinctive about the charts, which showed, in general, a fairly rapid return to normal recordings during the first day or two of hospitalization.

White-cell counts revealed a definite although slight leukopenia on the average. In 25 cases with all the clinical signs of influenza, the white-cell count ranged between 2600 and 9600, with an average of 5500. In the serologically studied group, counts in 6 cases ranged between 4100 and 8600, averaging 5800, on admission. In 1 case a white-cell count of 7600 on admission was found to be 4800 during the height of the illness, with a return to 8300 before discharge.

During the outbreak, there were remarkably few clinical complications. Three patients were diagnosed as having a hemolytic streptococcus pharyngitis, the organism having been cultured from their

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throats. This organism was also isolated from the throats of 3 of 21 other patients, in whom cultures were taken, for the most part toward the end of the outbreak. The first 3, with a moderate leukocytosis, as demonstrated by an average white-cell count of 12,100, were given chemotherapy. Of the 11 cases of otitis media, only 1 became purulent and required chemotherapy. White-cell counts

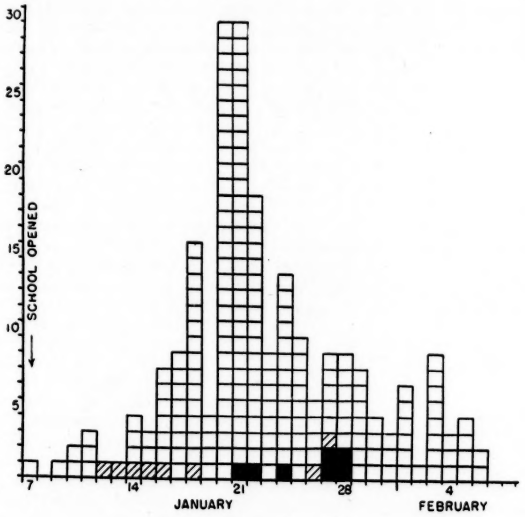

FIGURE 1. *Incidence of Cases.*

The empty squares represent case admitted because of upper respiratory infection; the cross-hatched squares, those tested for complement-fixing antibodies during the convalescent stage; and the black squares, those tested for complement-fixing antibodies during the acute and convalescent stages.

taken in 6 of these cases ranged between 7800 and 28,200, averaging 16,500. The 3 cases of pneumonia were clinically similar to so-called "primary atypical pneumonia of unknown etiology," but the patients had relatively high initial white-cell counts (average 18,500) that remained elevated for several days and then responded to penicillin.

Serologic studies were made in 8 cases during the convalescent stage, twelve to seventeen days after the onset of symptoms (Group 1), and in 7 others during both the acute, that is, the first three days, and convalescent stages (Group 2). Patients in the former group are indicated in Figure 1 by cross-hatched squares, and those in the latter by black squares.

Complement-fixation tests were carried out with the use of the allantoic fluids from embryonated eggs infected with the PR8 strain of influenza A or the Lee strain of influenza B; the procedure has been described elsewhere in detail.[1] In Group 1 the average final titer, determined as the reciprocal of the final dilution of serum before the addition of sensitized cells, was definitely elevated against influenza A — 1:421, or over twice as high as the titer of 1:192 (1:64 in the initial dilution of serum) regarded by Eaton and Rickard[2] as presumptive evidence of recent infection. Furthermore, 7 of the 8 patients tested showed titers of 1:192 or higher. The average titer against influenza B was 1:57, and in 1 case the titer was elevated, being 1:384.

In Group 2 the average titer against influenza A was approximately ten times as high in serums taken in the convalescent phase of the infection as in those taken in the acute phase, — 1:495 in the former and 1:42 in the latter, — and in 5 cases the titer increased fourfold or more following recovery. The average titer against influenza B was 1:9.0 in the convalescent and 1:0.9 in the acute phase. In only 1 case was there an increase in antibody reaction to influenza B, and in this case the titer during convalescence was relatively low, making the interpretation of the test uncertain.

Discussion

The results of the complement-fixation tests in Group 1 alone afford presumptive evidence for regarding the outbreak as predominantly due to influenza A. With one exception, no titer as high as 1:192 was obtained for influenza B. Although infections caused by influenza B had been prevalent in the eastern United States about two months previously, with this one exception, only extremely low concentrations of antibody, or none at all, were demonstrated. More conclusive serologic evidence that the outbreak was due to influenza A is afforded by the results of the tests on the 7 patients in Group 2.

Since an etiologic diagnosis of influenzal infection is at best equivocal on clinical criteria alone, it is of interest to compare clinical diagnoses in the serologically proved cases with those made during the course of the whole outbreak (Table 1). Although

Table 1. *Diagnoses in All and in Serologically Positive Cases.*

Diagnosis	All Cases		Serologically Positive Cases	
	No. of cases	Per-centage	No. of cases	Per-centage
Otitis media ...	11	5	1	7
Common cold...	87	40	5	33
Influenza.....	97	45	9	60

the number of serologically tested patients was small, it represented a rough cross section of the outbreak. Accordingly, the variations in clinical diagnosis appeared to reflect for the most part variations in the symptomatology rather than in the etiology of the disease.

It will be observed that during the outbreak, almost as many common colds were diagnosed as were cases of influenza. Of the 50 boys carefully questioned, 28 per cent regarded themselves as merely suffering from a cold and as doing the sensible thing by reporting to the infirmary. That this commendable attitude was not altogether a lofty application of principles of preventive medicine is suggested by the fact that four times as many boys reported on Sundays — usually in the late afternoon — and Mondays as on Saturdays. (The numbers reporting on different days of the week, beginning Saturday, were 11, 46, 45, 32, 22, 26 and 33.) The questionnaire was directed only to the hospitalized group, however, and it is evident that any infected boy who did not feel sick enough to report to the infirmary, if he had any symptoms at all, regarded himself as merely suffering from a cold. One of the three authors had a cold during the outbreak, but was able to continue working; another had influenza, requiring him to go to bed for a few days.

Although this work is in no sense meant to be construed as a study of "colds," it is pertinent to stress the fact that almost half the patients, as diagnosed by both medical and lay criteria, had common colds. These findings serve to emphasize earlier observations that clinical symptoms of different types of respiratory infections may overlap so much that the clinical differentiation is generally unreliable.[3] It is apparent that a cold may be both a symptom and a sign, and that even the diagnosis "common cold" is symptomatic rather than etiologic.

Finally, it is of interest, in view of our findings, to refer to the epidemiologic prediction of the Fort Bragg Commission on Acute Respiratory Diseases[4] based on observations of the cyclic character of influenza outbreaks. The commission stated that the probabilities were seven out of eleven that influenza A would reappear during the winter of 1945–1946. This reappearance of influenza A in what up to midwinter had been an influenza B year is all the more interesting in that the "present theory" of the commission also called "for a widespread epidemic [of influenza B] before the summer of 1946."

Summary

An epidemiologic and clinical description of upper respiratory infections occurring in a boys' boarding school in January and February, 1946, is given.

Complement-fixation tests were made for influenza A and B on the serums of 8 boys during convalescence and of 7 others during both the acute and convalescence phases. The average titer against influenza A among the convalescent patients was found to be more than double that considered presumptive evidence of recent infection. When the seven paired serums were tested, the average titer during the convalescent phase was found to be approximately ten times as high as that during the acute phase.

On the basis of the serologic evidence in this outbreak, the virus of influenza A appeared to be the predominant etiologic agent.

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RADIATION TREATMENT OF LOCALIZED MALIGNANT LYMPHOMA*

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THE term "malignant lymphoma" has been rather generally accepted, in America at least, to designate malignant tumors that are characterized by progressive enlargement of lymphoid tissue in various parts of the body. Pathologists have subdivided this group on a histologic basis into several more or less characteristic types. Clinically, the disease as a rule progresses with a varying degree of rapidity to a fatal termination, the average duration of life being from two to three years.[1] Gall and Mallory[2] reported 10 cases with survival, free of disease, for six years or more after surgical removal. In a more recent paper, Gall[3] added to the number. Jackson and Parker[4] report survivals up to twenty-four years, and others[1] claim fairly long survival rates.

That a certain number of patients with malignant lymphoma have been cured of their disease there can be no doubt. What are the factors responsible for these unexpected, favorable results, and can the same results be obtained with properly applied irradiation as with surgical procedures? It is with these questions that the present paper is concerned.

As in other types of malignant tumors, cure in malignant lymphoma may be assumed to depend on the extent of the disease at the time treatment was undertaken, as well as on the histology, the location of the tumor and the effectiveness of the treatment. Experience has shown that widely disseminated malignant tumors are not curable by any method of treatment at present available. Cure seems to depend on complete removal or destruction of the primary tumor before it has had an opportunity to spread beyond its immediate site.

Is there a time in the life history of a malignant lymphoma when it, like other forms of malignant tumors, may be considered a localized disease? Recent opinion seems to favor an affirmative answer to this question. Gall reports a patient who died of intercurrent disease four and a half years after the successful surgical removal of a follicular lymphoma of the inguinal lymph nodes. Autopsy failed to show any evidence of lymphoma. Further confirmation of this assumption is obtainable from a review of all patients who have survived, free of disease, for long periods. In nearly all such cases a localized lesion was present when treatment was undertaken.

On the supposition that the preceding hypothesis is correct, we have reviewed the records of approximately 500 patients with malignant lymphoma treated at the Massachusetts General and the Collis P. Huntington Memorial hospitals, and selected for particular study only those who were alive and apparently free of disease five years or longer in whom the lesion at the time of treatment was localized and who were treated with irradiation only, biopsy excepted. We have attempted to determine whether the favorable results in this group were due to the type of the lesion, the location of the lesion or the method of treatment, or whether no explanation could be obtained.

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Histologic Classification

If the leukemias and the paragranuloma of Jackson and Parker[4] are excluded, two classifications are generally accepted in this community — that of Gall and Mallory[2] and that of Jackson and Parker. The classifications are as follows:

GALL AND MALLORY	JACKSON AND PARKER
Stem-cell lymphoma Clasmatocytic lymphoma	Reticulum-cell sarcoma
Lymphoblastic lymphoma Lymphocytic lymphoma	Lymphosarcoma
Hodgkin's lymphoma	Hodgkin's granuloma
Hodgkin's sarcoma	Hodgkin's sarcoma
Follicular lymphoma	Giant follicular lymphoma

It will be noted that, except for slight differences in nomenclature, there is no marked divergence in classification.

Material

We have been able to collect 15 cases in which the histories conform with the problem as outlined — a single lesion at the time of treatment (which consisted primarily of radiation), diagnosis established by biopsy and the patient living and free of disease more than five years after the last course of treatment. Table 1 gives the pertinent data on this group of patients. Five were males, and 10 were females. The youngest was ten, and the oldest fifty-eight years old, the average age being thirty-seven years. The location of the lesion varied. There were abdominal tumors, either in the mesenteric lymph nodes or in some part of the gastrointestinal tract, in 4 cases. The tumor was in the peripheral lymph nodes in 5 cases, the involved nodes being in the neck in 4 and in the groin in 1. The remaining tumors were in the tonsil in 2 cases, the larynx in 1, the parotid gland in 1, the femur in 1 and the skin in 1.

Histologically, there were 2 stem-cell, 1 clasmatocytic, 6 lymphoblastic, 3 lymphocytic and 1 Hodgkin's lymphoma, 1 Hodgkin's sarcoma and 1 follicular lymphoma.§

§Slides of all these tumors were reviewed microscopically in 1946 in the Department of Pathology, Massachusetts General Hospital.

The x-ray dosage given was 1000 r or less in 9 cases, between 1000 r and 2000 r in 4 and over 2000 r in 2; extensive radium treatment was given in 1 case.

Analysis of Factors

Location. The location of the tumor does not seem to be the predominant factor on which survival can be based, but it is of some importance. In 4, or about a third, of the patients the lesion was in the abdomen. This percentage is quite comparable to that found by Gall. In another 5 cases, the lesion was in the peripheral lymph nodes, and in the remainder, in various other locations. Among students of this disease, there is a general opinion that when malignant lymphoma is localized, particularly in the gastrointestinal tract — or in the long bones[5] — and can be completely removed, a cure may be expected in a fair percentage of cases. Our findings may be interpreted as confirming this belief. Otherwise, the location of the single lymphomatous tumor seems to be unimportant.

Histology. It is known that the duration of life in a given case is somewhat dependent on the type of tumor present, and one would expect the chance of permanent cure to be best in the slowly growing, less malignant tumors. The data presented do not confirm this supposition, but the number of cases is too small to warrant a positive statement.

Extent of lesion. No long survivals, apparently free of disease, occurred in patients with multiple lesions. Localization of the disease at the time treatment is undertaken is probably an essential factor for lasting cure.

Method of treatment. The work of Gall and Mallory appears to show that complete surgical removal may produce permanent cure, and our findings indicate that the same results may be obtained by irradiation, provided the dose is sufficient to destroy the tumor. The minimum dose that will produce this result is not known, and our data do not give additional information. The smallest dose given was 600 r, and the largest 3000 r. Some of the tumors must have been extremely radiosensitive and others quite resistant, unless it is to be assumed that in some cases recovery was spontaneous.

TABLE 1. *Data in Patients Apparently Free of Disease More Than Five Years after Treatment.*

Age	Sex	Pathological Diagnosis	Location of Tumor	Onset of Disease	Treatment and Dosage	First Treatment	Last Treatment	Last Examination	Survival since onset	Survival since treatment
yr.									yr.	yr.
55	F	Stem-cell lymphoma	Ileum	Oct., 1939	Radium (++++)	Nov., 1939	Feb., 1940	Dec., 1945	6 2/12	5 10/12
25	M	Stem-cell lymphoma	Cervical lymph nodes	June, 1932	X-ray (1200 r)	June, 1932	Dec., 1932	Dec., 1945	13 6/12	13
17	F	Clasmatocytic lymphoma	Femur	Dec., 1935	X-ray (3000 r)	Aug., 1936	Aug., 1936	July, 1946	10 6/12	9 10/12
10	F	Lymphoblastic lymphoma	Cervical lymph nodes	Mar., 1932	X-ray (400 and 800 r)	Apr., 1936	Apr., 1940	Dec., 1945	13 9/12	5 8/12
44	F	Lymphoblastic lymphoma	Mesenteric lymph nodes	Oct., 1939	X-ray (1200 r)	Jan., 1940	Mar., 1940	Mar., 1946	6 5/12	6
41	F	Lymphoblastic lymphoma	Larynx	Oct., 1932	Radon seeds (10) X-ray (900 r)	Apr., 1933	Apr., 1933	Apr., 1946	13 6/12	13
57	F	Lymphoblastic lymphoma	Skin	June, 1934	X-ray (900 r)	Aug., 1934	Sept., 1934	July, 1944	10 1/12	9 10/12
58	F	Lymphoblastic lymphoma	Tonsil	Apr., 1937	X-ray (3000 r)	May, 1938	Apr., 1940	Mar., 1946	8 11/12	5 11/12
12	M	Lymphoblastic lymphoma	Cervical lymph nodes	Dec., 1916	Radium (++++)	July, 1918	Dec., 1920	May, 1946	29 5/12	25 5/12
37	F	Lymphocytic lymphoma	Parotid gland	Jan., 1938	X-ray (600 r)	Nov., 1938	Dec., 1938	Nov., 1945	7 10/12	6 11/12
45	F	Lymphocytic lymphoma	Tonsil	Jan., 1938	X-ray (1500 r)	Feb., 1938	Jan., 1940	Feb., 1946	8 1/12	6 1/12
35	F	Lymphocytic lymphoma	Cervical lymph nodes	Aug., 1934	X-ray (900 r)	Sept., 1934	Sept., 1934	Oct., 1945	11 2/12	11 1/12
35	M	Hodgkin's lymphoma	Mesenteric lymph nodes	— 1926	X-ray (300 ma. min. and ½ erythema dose)	Apr., 1930	Jan., 1931	Mar., 1946	20	15 2/12
45	M	Hodgkin's sarcoma	Retroperitoneal lymph nodes	Oct., 1928	X-ray (300 ma. min. and 400 and 800 r)	Apr., 1930	May. 1936	Jan., 1946	17 3/12	9 8/12
22	M	Follicular lymphoma	Inguinal lymph nodes	Jan., 1937	X-ray (600 r)	Mar., 1937	Mar., 1937	Aug., 1945	8 7/12	8 5/12

CONCLUSIONS

Localization of the disease in malignant lymphoma, as in other malignant tumors, is a most important factor in suggesting a favorable prognosis.

Apparent clinical cure or remission may be obtained by irradiation as well as by surgical removal

if the destruction of the tumor is complete. The radiation dosage should be large enough to accomplish this. In some cases the dosage may be as little as 600 r, but as a rule it is wiser to give as much as the normal tissues will tolerate without undue damage. With supervoltage (1200 kilovolts) and heavy filtration, the dosage may be as high as 2000 r.

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MEDICAL PROGRESS

BIOCHEMICAL ABNORMALITIES DURING RENAL INSUFFICIENCY (Concluded)*

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Calcium and Phosphorus

Calcium and phosphorus are predominantly localized in bone, but both elements occur in the cell,[8] phosphorus being particularly important. Inorganic phosphate is the chief anion in the intracellular fluid, and the organic phosphates of the cell appear to have considerable significance in the metabolism of fats and carbohydrates, the energetics of cellular activity and the physiology of muscular contraction. The extracellular water content of calcium and phosphorus is small in absolute amounts, but it is vital in the maintenance of normal neuromuscular irritability and bone structure. In addition, both substances play a role in acid-base regulation of body fluids. As with the other electrolytes, both ions are constantly undergoing exchange and exist in dynamic equilibriums.[74, 75]

Calcium exists in the plasma in two forms — one completely ionized and highly diffusible, and the other bound to protein and indiffusible. A small proportion is also indiffusible because it is linked to phosphate and citrate in colloidal aggregates.[8] The inorganic phosphate of the plasma diffuses readily through collodion membranes and is apparently not bound to protein.[4, 76] About half the phosphorus in the plasma is incorporated in the molecules of various lipids and fatty acids that may participate in base binding.[77]

The plasma concentrations of ionic calcium and phosphate are resultants of the interaction of many factors. Chief among these are the relative concentrations of protein, hydrogen and bicarbonate ions. Moreover, calcium and phosphate levels tend to vary reciprocally under most circumstances for reasons that are not understood. It is now well established that the secretion of the parathyroid glands, parathormone, is influential in controlling the concentrations of both ions.[78] The manner in which parathormone accomplishes this is a matter of controversy. On the one hand, it is believed that parathormone reduces the phosphate concentration by decreasing its renal tubular reabsorption,[79, 80] the subsequent hypophosphatemia inducing hypercalcemia and mobilization of fixed calcium physicochemically, and on the other, that parathormone acts directly on the bone to mobilize calcium.[81, 82] There is evidence that both actions may occur.[83] Finally, normal calcium-phosphorus metabolism depends on adequate dietary intake and intestinal absorption. Vitamin D is essential to the latter.

Both calcium and phosphorus are important constituents of the glomerular filtrate. During the passage through the tubules, both are reabsorbed by separate mechanisms and conserved or discarded in accordance with the needs of the body and the demands of the various processes in which they participate.

Relatively little is known about the mechanism of tubular calcium reabsorption. The calcium in the glomerular filtrate, which is limited to the ionized fraction, apparently undergoes extensive reabsorption.[4] Hypercalcinuria results when calcium is injected intravenously[84] and during hypercalcemia in hyperparathyroidism.[85] These findings suggest that the reabsorptive mechanism can be saturated, but this possibility has never been examined quantitatively.

Convincing quantitative evidence that phosphate is removed from tubular urine by a mechanism of limited capacity is now available.[76] At high plasma levels of phosphate, the rate of reabsorption becomes constant and excess phosphate is lost in the urine. This maximal activity is inhibited by glucose reabsorption. Nevertheless, an independent mechanism is apparently involved since phlorhizination enhances phosphate reabsorption whereas it halts

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that of glucose. Parathormone is also considered to reduce phosphate reabsorption.[86] The phosphate salts in the urine play a significant role in the excretion of hydrogen ion, as pointed out above, but it now appears that acid-base imbalance has no influence on their tubular reabsorption.[76] It seems possible to explain claims to the contrary[87] on the basis of changes in the quantity of phosphate available for excretion rather than on the basis of renal functional alteration.

In renal insufficiency the reduction of filtration depresses the renal excretion of both phosphate and calcium. It is a curious, and thus far inexplicable, fact that only phosphate is retained, as a rule, in this situation. The retention of phosphate leads to depression of the calcium ion level and increased loss of calcium in the feces. The preferential retention of phosphorus may be accounted for on the basis of dietary imbalance, since the diet usually contains somewhat more phosphorus than calcium.[8] The renal excretion of calcium and phosphorus generally parallels the intake, but with loss of renal control it is possible that phosphorus accumulates more rapidly than calcium and thus sets in motion other reactions that produce hypocalcemia. This point of view is supported by the fact that low-phosphorus diets[88] or increased fecal excretion of phosphorus following the ingestion of precipitating agents, such as aluminum hydroxide,[89] may correct the calcium-phosphorus imbalance during uremia. The recent demonstration of phosphate mobilization during stress[90, 91] provides another possible explanation of hyperphosphatemia in uremia.

Hypocalcemia can develop, however, in the absence of phosphate retention, apparently as a result of impaired intestinal absorption.[85, 92] Since vitamin D does not wholly correct this defect, it has been suggested that inactivation of the vitamin may occur.

Tetany due to a diminished plasma concentration of calcium ions is a frequent feature of uremia. As a rule, its manifestations are mild, consisting of muscle cramps and twitching and hyperirritability of motor nerves. Occasionally, however, convulsive seizures occur. Mason and his co-workers[93] have found that tetany and convulsions follow the reduction of calcium ion concentration in the cerebrospinal fluid rather than in the plasma.

Bony abnormalities may develop in renal insufficiency of long duration associated with chronic acidosis. Growing children in particular may present striking changes resembling rickets, often with serious deformities due to maldevelopment, epiphyseal separation and pathologic fractures. Adults seldom suffer from a severe grade of skeletal involvement, but histologic alterations may be found in most cases. In addition, so-called "metastatic calcification" may occur. Mönckeberg's medial sclerosis or diffuse calcification may involve the arteries, and calcium plaques may appear in the subcutaneous tissues.[94, 95]

Medical writings on these subjects are conflicting and confused; little agreement has been reached regarding either the cause or the character of skeletal changes. This controversy is evident in numerous descriptive terms that include "renal rickets," "renal osteomalacia," "renal dwarfism," "renal hyperparathyroidism," "renal osteodystrophy" and "renal osteitis fibrosa."

It is generally agreed that protracted renal insufficiency, chronic acidosis, low plasma calcium concentration and phosphate retention are common to most of these cases. Moreover, parathyroid hypertrophy has been found in most cases when a careful search has been made at autopsy.[96] Regarding the character of the bone changes and their causation, however, opinion is sharply divided.

The difficulty of interpreting the physiology of certain other skeletal disorders that result in or apparently arise from renal dysfunction complicates the dispute still more. Hyperparathyroidism, caused either by parathyroid adenoma or by idiopathic diffuse hyperplasia of the parathyroid glands, may produce marked renal damage. The increased secretion of parathyroid hormone leads to increased renal phosphate excretion and, in turn, to hypophosphatemia, hypercalcemia and finally hypercalcinuria.[97] Calcification of the kidney tubules, the formation of calcium stones and the subsequent complication of pyelonephritis lead, in many cases, to fatal uremia.[98] Cystine-storage disease[99] likewise causes renal damage and bony abnormalities somewhat similar to those of rickets. Few cases have been reported, and nothing is known of the biochemical alterations. Cystine deposits and cystine calculi have been found in the kidneys. In contrast to these metabolic and endocrine disturbances are certain rare conditions in which anomalies of renal function lead to biochemical and skeletal defects that are different in some respects from those frequently seen in renal insufficiency. A few cases of renal glycosuria, hypochloremia, hypophosphatemia, hypocalcemia and acidosis, usually associated with dwarfism, have been reported.[100, 101] McCune, Mason and Clarke[100] suggest that this so-called "Fanconi syndrome" results from a developmental defect of the renal tubules that permits loss of glucose, phosphate and base. The chronic acidosis is considered to be the cause of the skeletal deformity. A somewhat similar disorder described in adults as well as in children,[101–104] in which renal damage appears to be secondary to deposits of calcium in the kidney, differs from the Fanconi syndrome in presenting hyperchloremia and in the absence of glycosuria. Albright and his associates[102] suggest that the primary defect is a tubular inability to secrete an acid urine, calcium taking the place of deficient base in the urine. Snapper[85] and others[92] have re-

ported cases among Northern Chinese that appear to resemble those usually described as renal rickets in which the plasma phosphate concentration remained low. All these conditions, and possibly some others, must be considered apart from the more frequent syndrome of hypocalcemia, hyperphosphatemia and acidosis that leads to bony distortions during protracted renal insufficiency.

In the controversy regarding renal rickets, it is evident that several areas of disagreement may be defined. In the first place, it appears that the name "renal rickets" may be misapplied, since most pathological studies have revealed that the bone lesion is identical with that produced by hyperparathyroidism — generalized osteitis fibrosa.[95, 108] It is agreed that the failure of epiphyseal closure seen on x-ray examination denotes a rachitic alteration, but on the whole the roentgenographic findings are not helpful in reaching a decision. Earlier workers[106] considered the bone lesion similar to that of rickets, but their descriptions tally, for the most part, with the pathological picture of osteitis fibrosa. Recently, Follis and Jackson[107] found microscopic changes in the bone in 19 of 39 cases of chronic renal insufficiency in adults, in most of which it appeared that broadening of the osteoid sheaths of the bone trabeculae and increased bone destruction, with replacement by fibrous tissue, occurred simultaneously. They interpreted these changes as evidence of coexistent osteomalacia and osteitis fibrosa, and claimed that osteomalacic alterations were predominant. These conclusions are in disagreement with those of Ginzler and Jaffe[105] in a similar series and await confirmation. In general, the mass of evidence favors the view that osteitis fibrosa is the typical lesion.

The discovery of parathyroid hyperplasia, together with the demonstration of osteitis fibrosa, in many of these cases, has elicited enthusiastic claims that the condition should rightfully be called "renal hyperparathyroidism" and that excess production of parathormone is responsible for the bone lesions.[108, 109] The weight of the evidence now available in the literature appears definitely to favor the view that parathyroid hormone may cause decalcification of bone in experimental animals after bilateral nephrectomy,[83] but it is also clear that the development of acidosis contributes heavily to the process of bone resorption. Hence, it is possible that parathormone is active in chronic renal insufficiency, but it cannot be accounted the chief cause of bone change. Since it has been pointed out that the histology of secondary parathyroid hyperplasia differs strikingly from that of primary disease,[96] it is possible that parathormone production in man is in no way comparable to the dosage administered nephrectomized rats, as described by Ingalls et al.[83] The causes for secondary hyperplasia remain obscure, attention having been paid to hypocalcemia,[95] hyperphosphatemia,[110] total calcium-phosphorus imbalance[108] and acidosis.[85] It has been suggested that the hypertrophy represents compensation rather than overactivity, in response to the need for maintaining the ionic calcium content of plasma.[95]

Since acidosis is always present and since acidosis and a low-calcium diet have been found to produce osteitis fibrosa in experimental animals,[111] it seems not unlikely that chronic acidosis may be at the root of the disorder. This factor would be expected to result in mobilization of calcium from the bones and, in the presence of renal insufficiency, in a reduction of the absorption of calcium from the bowel. Ginzler and Jaffe[105] suggest that periods of fluctuation of renal insufficiency and acidosis with new-bone deposition, followed by further resorption, may be expected to produce the degree of osteosclerosis they observed in their series. In line with the view that insufficient calcium absorption occurs are the findings that vitamin D administration occasionally results in improvement[92] and that the fecal loss of calcium is too small to arise from excessive withdrawal from bone.[95] It seems more probable that a persistent reduction of calcium absorption is operative.

A somewhat different type of osseous abnormality, compatible with normal growth, has been described in nephrotic children. Emerson and Beckman[112] have consistently found hypocalcemia, mainly attributable to a deficiency of the protein-bound fraction, in these patients associated with rarefaction of the diaphyses of bone. No abnormality of epiphyseal calcification was noted, however. For some reason, calcium uptake from the bowel was markedly reduced and renal excretion of calcium fell, apparently as a result of the need for calcium conservation. This metabolic abnormality has been described in other cases.[113] The changes often cleared during remissions of the disease, when the plasma protein concentration returned toward normal.

Other Electrolytes

So far as their relative plasma concentrations are concerned, the remaining electrolytes of the body fluids are unimportant. Moreover, so far as knowledge goes, it appears that these substances acquire little added significance during renal insufficiency, although it must be admitted that the information at hand is unsatisfactory, since these substances are difficult to determine.

Sulfate retention is known to occur[114, 115] and probably contributes to acidosis. This ion is excreted efficiently by the kidney, undergoing little reabsorption during its passage through the tubules.[116] It is interesting that sodium chloride excretion is depressed when sulfate ions are present in excess, and it is possible that this is a contributing factor in certain cases of salt retention. Sulfate

is retained early in the course of renal insufficiency and has been suggested as a more reliable index of renal failure than the concentration of most other substances.[114]

Magnesium, likewise, often accumulates in the blood during renal insufficiency, but it appears that the concentrations attained are never sufficiently high to evoke symptoms on the basis of its own pharmacologic activity.[117–119]

Nonelectrolytes

Most of the solid matter in solution or in colloidal suspension in the plasma is organic and nonelectrolytic in nature. These substances vary widely in complexity from the small molecule of urea to the highly intricate structures of the various plasma proteins and fats. In general, they comprise what has been termed the "metabolic pool," existing in equilibrium, like the electrolytes, with similar substances within the cells and readily available for use in various intracellular reactions. Certain substances, like creatinine and urea, appear to be end products of metabolic processes and must be removed from the body,[8] whereas others are essential to the construction of more complex compounds or to the development of energy for use by cells and must, therefore, be conserved. The kidneys are important in the maintenance of the plasma composition of many of these substances either by providing a route of active excretion or by preventing their loss in the urine.

Relatively little is known of the factors that govern the plasma concentrations of most of these compounds. The methods of chemical analysis are unsatisfactory and often difficult. In fact, a relatively large residue of organic material in the blood and urine remains unanalyzed. Moreover, the intracellular reactions in which organic compounds participate cannot be examined directly. Despite this paucity of knowledge, or perhaps because of it, there has been considerable speculation regarding their activity during renal insufficiency.

In general, these compounds fall into three groups from the standpoint of renal physiology. Large complex molecules that cannot pass the glomerular filter, such as proteins and fats, do not appear in the filtrate except during renal disease. Under these circumstances protein and lipoidal substances may be lost in the urine. In addition, it appears that abnormal renal cellular activity may provoke a general disturbance in fat[120] and protein metabolism.[121] A second group of substances, including glucose and the amino acids, appear in the glomerular filtrate and are so actively reabsorbed that little is lost in the urine. Curiously enough, an excessive loss does not usually occur even in advanced renal insufficiency. The third category, however, composed of diffusible waste products, including urea, creatinine and uric acid, is normally excreted in large amounts in the urine and accumulates in the blood when the filtration rate is reduced.

The retention of organic catabolites in the blood during renal insufficiency was discovered shortly after Bright's demonstration of the relation between renal disease and uremia. The hypothesis that the symptomatology of uremia is based on an intoxication by these substances was immediately developed and has continued to occupy a prominent position in discussions of renal insufficiency. But little direct and trustworthy evidence has been brought forward in support of this thesis. Each of a number of substances has been advanced as the sole cause of symptoms. More recently, emphasis has been placed on the possibility that the retention of several toxic agents is involved.[122, 123] It is tacitly or explicitly implied in most studies, however, that the uremic syndrome arises from a toxemia. In the light of the increasing knowledge of the metabolic imbalance during renal insufficiency, this viewpoint seems oversimplified. Certainly, the serious disturbances of body water and electrolytes must play a role in causing symptoms. Likewise, it seems probable that a general disorder of all metabolic activity, arising from the abnormalities of plasma catabolite concentrations among others, is involved. In this view, the increased concentrations of such substances as urea, creatinine, phenol and guanidine are important not because of the pharmacologic action of each but because of the interference with many intracellular reactions in which they participate. For this effect, none of them need be present in the blood in toxic amounts.

Nonprotein Nitrogen

It is well known that the nonprotein nitrogen content of the plasma increases, as a rule, with renal insufficiency. This change has come to be regarded as the hallmark of renal failure, although occasionally azotemia fails to develop even in far-advanced renal disease.[124]

The nonprotein nitrogen of the blood is derived from many sources, among which urea, creatinine, uric acid and the amino acids are most significant. The plasma concentrations of these compounds, with the exception of the amino acids and possibly other substances that contribute little to the total nonprotein nitrogen, depend on a balance between tissue breakdown, intracellular metabolic processes and diet on the one hand and renal excretion on the other. Thus, azotemia develops when this balance is deranged by a failure of renal excretion or by an increase in the production of nitrogenous substances, or both.

Recent studies indicate that a negative nitrogen balance develops in the presence of unusual stress.[125, 126] Excessive nitrogen loss, which occurs during fever, after trauma or operative procedures

and during shock, cannot be prevented by dietary measures[127] and is apparently not attributable to tissue destruction or disuse atrophy.[125] It has been suggested[128] that this phenomenon is related to Selye's[129] "alarm reaction" and may possibly be due to excess secretion of the so-called "S hormone" by the adrenal cortex. It is entirely possible that similar factors are operative in some cases of renal insufficiency and account, in part, for azotemia. Certainly, the characteristic wasting is attended by mobilization of nitrogen and negative nitrogen balances have been observed in chronic renal disease.[130] From a therapeutic standpoint, it is interesting that desoxycorticosterone appears to retard the elevation of nonprotein nitrogen in nephrectomized rats.[73]

Urea

Urea mounts in the blood following a reduction of glomerular filtration rate more rapidly than other nitrogenous substances and makes up an increasingly larger fraction of the nonprotein nitrogen. Tubular reabsorption of urea appears to be passive, increasing as the urine flow falls.[131] It is not surprising, therefore, that urea retention should be prominent when filtration reduction is only moderate, since the slowing of the stream of glomerular filtrate permits a larger fraction of the urea to return to the blood by diffusion. An adequate correlation between the filtration rate and the plasma urea concentration, however, does not obtain throughout the course of renal disease.[124] Indeed, the urea level may remain essentially normal until renal insufficiency is marked. This behavior apparently depends on several factors. Tubular diuresis may decrease urea reabsorption and counteract in a small way the effect of defective filtration. But it seems likely that decreased ingestion of protein, as a result of anorexia, is more important in preventing elevation of plasma urea. Moreover, it is possible that urea production is diminished.[132]

It has been proved that urea is relatively nontoxic in the concentrations usually found in uremia.[133] Indeed, patients with blood urea nitrogen concentrations persistently above 200 mg. per 100 cc. may pursue active lives for several years. It has been suggested, however, that urea interferes with detoxification in the body and permits the accumulation of more toxic substances.[122]

Creatinine and Guanidine

Creatinine, like urea, appears to be an end product of metabolism that lies outside the metabolic pool.[3] These compounds cannot be used by the cells in any manner and must be removed from the body as they accumulate. The addition of creatinine to the blood, however, is relatively slow, and its plasma level does not rise proportionately as high as that of urea.[134, 135] Hence, creatinine retention tends to occur only after renal disease is far advanced and is therefore considered to have greater prognostic significance than urea. This phenomenon is possibly based, in part, on the fact that in man creatinine is excreted by tubular activity as well as by filtration.[136]

Guanidine, a highly toxic compound related to creatinine, has aroused considerable interest because of studies indicating an increase of this substance in the blood during uremia that parallels the development of the symptoms.[93, 137, 138] But it does not follow that this relation is causal, nor has it been proved that the blood guanidine even reaches a toxic level, since the methods of determining it are unsatisfactory and relatively nonspecific.

Uric Acid

The degradation of nucleoproteins in man ends in the production of uric acid, which is excreted in the urine after filtration through the glomerulus and partial reabsorption by the tubules. The details of the metabolism of this curious substance remain unsolved. It possesses unusual physiochemical properties that give it value in water conservation among reptiles and birds,[4] but that are apparently of little benefit to man. In gout, deposits of the material in synovia and cartilage are associated with abnormalities of its excretion, hyperuricemia and arthropathy. Likewise, uric acid accumulates in the plasma during renal insufficiency, but whether this circumstance is responsible for goutlike episodes of synovitis, bursitis and arthritis is unknown.

It has been claimed that uric acid is retained in the blood during renal insufficiency earlier than any other substance and that such retention has considerable value from the diagnostic viewpoint.[134, 135] This claim has been disputed,[139] but it appears to be true for many cases. It is of great interest that hyperuricemia may be one of the earliest evidences of pre-eclampsia.[140] Chesley and Williams[141] have found that this phenomenon is caused by a reduction of uric acid clearance secondary to a decrease in the glomerular filtration rate and an increase in tubular reabsorption rather than by a change in metabolism, as others have claimed.[140]

Glucose

Glucose is typical of the second group of substances discussed above. It is reabsorbed from the glomerular filtrate almost completely. This process of conservation is rarely disturbed even in advanced renal disease when water and salt are lost in abundance. Rarely, renal glycosuria does occur, but for the most part the reduction in filtration rate appears to outstrip the reduction in tubular activity so that the capacity for glucose reabsorption is not exceeded. A disturbance of carbohydrate metabolism, however, has been demonstrated by Linder, Hiller and Van Slyke.[142] In far-advanced renal disease, an abnormal blood sugar curve was found following the ingestion of glucose. The glucose con-

centration reached a higher level than normal and returned slowly to the control value. Since no abnormality of the respiratory quotient was demonstrable, it was concluded that some factor other than a failure to burn glucose, such as retarded glycogen storage, was responsible. In the absence of renal failure the glucose tolerance was normal. This defect of carbohydrate metabolism is in line with the view that uremia arises from a general metabolic disturbance.

Amino Acids

The amino acids are also reabsorbed efficiently, and if retention occurs it apparently stems from an abnormality of liver function. Lyttle and his coworkers[143] have given intravenous injections of casein hydrolysate to children with renal disorders and have studied the rate of return of amino acids in the blood to a normal level. They found that normal removal from the blood occurred in spite of the presence of renal insufficiency. In children with hepatic disease and normal renal function, however, the removal of amino acid was greatly retarded.

In this study, it was found that the nephrotic syndrome was characterized by normal uptake of amino acids, in harmony with the work of others.[144] But an augmentation of amino acid removal from the blood has been observed shortly before the onset of the so-called "nephrotic crisis," with the subsequent development of hypoaminoacidemia.[145] The causes for the negative nitrogen balance and loss of amino acids in this situation are obscure. It appears that the parenteral administration of casein hydrolysate corrects the disturbance of nitrogen balance to some extent and apparently produces a significant reduction of fatalities due to bacteremia during the crisis.[146] Farr[144] attributes the loss of nitrogen to toxic nitrogen metabolism. It is not clear whether the loss of amino acids in the urine is a factor.

It should be understood that the methods now available for studying the amino acids of the blood are unsatisfactory and that what has been said about them has reference, for the most part, to the alpha amino acids detected by the ninhydrin method. Other methods are available for the determination of many individual acids. The use of these procedures in studies of the behavior of different acids during renal insufficiency should elicit much interesting information.

Phenols

The discovery that phenolic compounds accumulate in the blood during uremia has aroused considerable interest.[147–150] These substances are believed to be derived largely from the degradation of aromatic amino acids in the intestine. Free phenols are extremely toxic, causing renal damage and central-nervous-system depression. Harrison[122] suggests that they are responsible for certain of the neuromuscular phenomena observed in uremic animals. The methods used in determining the concentrations of phenols in the blood, however, are nonspecific and unreliable. The chief argument in favor of the importance of these substances in the production of uremia lies in the fact that a good correlation has been found between symptomatology and phenol accumulation. This need not imply a causal relation, however.

There is little evidence to support the view that other toxic products of intestinal putrefaction, such as indican, are of any significance in uremia.[151, 152]

Plasma Proteins

Protein is lost in the urine throughout most of the course of renal insufficiency, probably owing to increased passage of large molecules through the defective glomerular filter, although there is evidence that diminished tubular reabsorption of protein is also at fault.[153] The character of the urinary protein complies with the view that an increase in the size of glomerular pores permits smaller species of protein molecules, particularly albumin, to escape from the plasma. When this loss is excessive, hypoproteinemia develops. It appears that urinary loss is not sufficient to account for the diminution of protein in most cases, however, and a disturbance of protein manufacture must be posited.[121] Since protein escape is reduced by the contraction of the glomerular filter bed with progressive renal damage, hypoproteinemia is gradually corrected, and during the terminal stages of uremia, it is not a prominent feature.

The study of the plasma proteins is still in its early stages. New methods have been developed and have not yet been extensively applied to the investigation of renal disease.

Lipids

It has been shown that renal damage not only permits the escape of lipoidal compounds in the urine but also leads to lipemia and hypercholesterolemia. For reasons as yet unknown, this disturbance of fat metabolism is most profound in the presence of hypoproteinemia and may be related to it in some way. As renal failure progresses, these abnormalities regress.[120, 154, 155]

* * *

Throughout this discussion, an effort has been made to emphasize the complex nature of biochemical disturbances during renal insufficiency. This complexity arises from the simultaneous derangement of metabolic activities of all types throughout the body and is secondary to the disorder of plasma composition resulting from the failure of the kidney to perform its regulatory functions. It is probable that the symptomatology of uremia is the result of the action of multiple

factors, among which the change in the character of the metabolic pool bulks large.

The attempt to find toxic agents retained by the diseased kidney to account for various symptoms has not been fruitful. No evidence that the kidney manufactures toxic substances has been elicited,[156] and the evidence suggesting that intoxication by products of intestinal putrefaction occurs is not convincing. It may be that substances as yet undetermined play an important role, but there seems to be ample cause for symptomatology in the disturbances that have been subjected to quantitative study.

Obviously a considerable amount of work remains to be done. At present, the factual knowledge of normal processes is faulty and incomplete, and it is not surprising that a satisfactory understanding of the abnormalities has not yet been attained. As methodology improves and factual data accumulate, however, rapid strides on the conceptual level may be confidently expected.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 32481

PRESENTATION OF CASE

First admission. A thirty-eight-year-old Italian clerk entered the hospital because of a swelling below the right eye, which he suspected of being a "cancer."

For three years before entry the patient had noticed many small, spidery, red spots on the cheeks, abdomen and flanks. These never increased in size or caused him any concern until two months before entry, when one of these spots beneath the right eye began to enlarge. Except for this condition, the patient considered his health excellent. He had had a slight, nonproductive cough following an attack of pleurisy eighteen years previously. Since the age of nine years he had also had an occasional slight purulent discharge from the right ear. He had observed no swelling of the abdomen, jaundice, hemorrhoids, varicose veins or ankle edema. The alcoholic intake was impressive, amounting to at least a bottle of wine a day since childhood and an additional daily consumption of about a quart of whiskey and several bottles of beer for the preceding eight years. Nevertheless, he insisted that his diet was "good" and his appetite keen. The weight had remained constant for the past seventeen years. The urine had been orange on occasion, but the stools had always been brown.

The patient was a well developed and well nourished man with fine spider angiomas over the chest, upper abdomen and flanks. Below the right eye there was an angioma 2 cm. in diameter with a slightly raised red antrum 3 mm. in diameter. The heart and lungs were clear. The abdomen was protuberant and soft, with a questionable fluid wave but no shifting dullness. The liver edge was readily palpable, extending 12.5 cm. below the costal margin in the anterior axillary line, but was firm and nontender.

The temperature, pulse and respirations were normal. The blood pressure was 140 systolic, 85 diastolic.

The blood van den Bergh reaction was 2.7 mg. per 100 cc. total. The cephalin-flocculation test was ++++ at the end of twenty-four hours. A bromsulfalein test showed 35 per cent retention of the dye. The total serum protein was 7.6 gm. per 100 cc., with an albumin-globulin ratio of 1.5. The urine gave a +++ test for bile and green, blue and orange reactions for sugar on three occasions. The stools were guaiac negative.

A gastrointestinal series and chest plates were essentially negative.

Peritoneoscopy revealed a large "hobnail" liver, and a biopsy specimen was reported as showing advanced toxic cirrhosis.

The patient was discharged with instructions to abstain from alcohol and to follow a high-vitamin, high-carbohydrate, high-protein, high-calorie and low-fat diet.

Final admission (four and a half years later). The patient was followed in the Out Patient Department and apparently did well although he noticed slight swelling of the ankles at night; he had a dirty-gray color. He claimed to have restricted his drinking to about four highballs a day. A month before entry he began work as a night watchman and

felt unusually tired and sleepy. On the day of entry, he developed chills and fever while at his job and was brought to the emergency ward via ambulance. On arrival he also noted "dizziness" and swaying from side to side while walking. The right ear had recently been draining purulent material, but this was no different from many previous episodes.

The patient appeared acutely and chronically ill. He was drowsy and dozed off several times during the examination. The skin was hot and dry and showed a grayish icteric pigmentation, most marked in the exposed areas. There were numerous spider angiomas. A skin test for iron pigment was negative. The pharynx and soft palate were beefy red, with a mucous coating over the posterior portion. The right ear canal contained blood-tinged, seropurulent discharge. There were a few rales at the left base. A Grade II apical systolic murmur was transmitted over the entire precordium. The aortic second sound was louder than the pulmonic. There were shifting dullness over the abdomen and a questionable fluid wave. The liver edge was palpable 4 fingerbreadths below the costal margin. Moderate muscle weakness was apparent in all extremities, and vibratory sense in the legs was absent.

The temperature was 100.4° F., the pulse 100, and the respirations 24. The blood pressure was 110 systolic, 60 diastolic.

Examination of the blood showed a red-cell count of 4,840,000, with 15 gm. of hemoglobin, and a white-cell count of 20,200, with 92 per cent neutrophils. The fasting blood sugar was 190, the nonprotein nitrogen 30 and the phosphorus 2.5 mg. per 100 cc., the alkaline phosphatase was 6.1 Bodansky units per 100 cc., the sodium 128.4 milliequiv. per liter and the serum protein 5.8 gm. per 100 cc., with an albumin-globulin ratio of 0.8. The van den Bergh reaction was 5.6 mg. per 100 cc. direct and 10.0 mg. total. The cephalin-flocculation test was ++++ in twenty-four hours. The prothrombin time was 30 minutes, with a control of 18 minutes. *Staphylococcus aureus* was grown on two consecutive blood cultures. The urine was dark amber, with a specific gravity of 1.014. There was a green test for sugar and a ++ test for bile but no albumin. The sediment contained many white cells, red cells and granular casts per high-power field.

An x-ray film of the chest showed enlargement of the heart, particularly in the region of the left ventricle and left auricle. The diaphragm moved only slightly. The lung fields were clear. There was a suggestion of small varices in the lower third of the esophagus.

An electrocardiogram showed a rate of 95, with sinus rhythm. The PR interval was 0.18 second and the QRS complex 0.08. The voltage was normal, and there was no deviation of the axis. The T waves in Leads 1 and 2 were unusually broad and rather low.

The temperature gradually returned to normal on penicillin therapy, but the pulse rate was continuously elevated; the patient frequently lapsed into a semicomatose or delirious state. The dosage of penicillin was 24,000 units every three hours for six days and was increased to 32,000 units every two hours for the remainder of the illness. A lumbar puncture showed an essentially normal fluid with normal dynamics. During the ten days in the hospital the patient gained 22 pounds, which was apparent as pitting edema over the dependent portions and increasing ascites. On the seventh hospital day a Grade II diastolic murmur to the left of the sternum was discovered. The patient was digitalized and given Mercupurin. Nevertheless he continued to gain fluid. A Prussian-blue skin test for hemochromatosis was negative in two injection sites. On the sixteenth hospital day the patient was found unresponsive, with Cheyne–Stokes respirations, and he died shortly thereafter.

Differential Diagnosis

Dr. James Townsend: There is no record of a blood sugar determination or a blood Hinton test during the first admission four and a half years previously or of any test for sugar in the urine in any of the visits to the Out Patient Department between the admissions. Certain things in the clinical history are worthy of emphasis. The alcohol intake described is enormous, amounting to 6000 calories a day. Under these conditions it is improbable that the patient had a normal food intake, and he might therefore be considered a fit subject for avitaminosis. Secondly, spider angiomas were noticed on both admissions. These, if typical, are important findings, believed by many to be pathognomonic of Laennec's cirrhosis, but I am sure that they occur in other types of liver diseases; the most characteristic ones that I have seen occurred in a case of prolonged infectious hepatitis that began during an epidemic among the American forces in Italy. Thirdly, convincing evidence of toxic cirrhosis four and a half years previously was provided by the various chemical tests as well as by direct vision of the liver and biopsy. The chemical findings at the time of the final admission are consistent with a gradual progression or recent exacerbation of the cirrhosis. Fourthly, there was definite evidence of enlargement of the heart since the first hospitalization, as well as new murmurs, both systolic and diastolic, not previously described. Finally, the finding of a low serum sodium is worthy of note. There are two conditions that are usually associated with a low sodium — Addison's disease and severe dehydration. In this case there is no evidence of dehydration.

It seems to me that the following were the most significant findings in this long and rather complicated picture. A definite diagnosis of toxic cirrhosis was made four and a half years before the final entry, with evidence of progression of the disease during

the illness as shown by the ascites, the hypoproteinemia and the possible esophageal varices and of glycosuria at that time and during the final illness. Could the last finding be attributed to cirrhosis? There is a carbohydrate disturbance in cirrhosis, but — except after the injection of glucose — sufficient sugar in the urine to give an orange reaction is unusual. It would be extraordinary to have a fasting blood sugar as high as 190 mg. per 100 cc. Therefore, I believe that this man had diabetes, probably of several years' duration, and that autopsy may have revealed some of the findings that are found in patients with chronic diabetes, usually in the vascular system, with the glomeruli showing changes characteristic of Kimmelstiel-Wilson disease and other vascular disturbances. The patient had a chronic middle-ear infection for many years, and the symptoms of acute illness began a month before the final admission, when he had fever and a discharge from his ear that increased on the day of entry. He was given a course of penicillin. New heart murmurs, both systolic and diastolic, were noted, with cardiac enlargement that had not been present four years earlier, and *Staph. aureus* was grown on two blood cultures. He also had abnormal urinary findings, but without albumin, and a normal nonprotein nitrogen.

There seems to be no room for argument against cirrhosis of the liver. The clinical picture was quite characteristic, and I think we may assume that the disease either progressed in spite of treatment or became exacerbated during the final illness. I believe that the patient still had severe cirrhosis of the liver of the Laennec type. Could it have been some other type? This man had the triad of peculiar color of the skin, diabetes and liver disturbances. Hemochromatosis comes to mind. Tests were done for that, but they were negative. There was even a negative skin biopsy, and I doubt whether hemochromatosis was apparent clinically. In the few cases that I have seen the only characteristic finding has been severe diabetes, which is difficult to control in spite of large doses of insulin. If this man had diabetes, it was mild and chronic. I believe that he had diabetes mellitus in addition to the cirrhosis of the liver.

He also had a chronic suppurating process in the right ear, which I believe had much to do with the onset of the final illness. I should like to believe that it was the portal of entry of the *Staph. aureus* that was found in the blood stream. There is considerable evidence to support the diagnosis of bacterial endocarditis because of the finding of new heart murmurs, the presence of cardiac enlargement and the progressively fatal course in spite of a fair amount of penicillin. If he had bacterial endocarditis, other areas of staphylococcal infection may have been observed in the kidneys and possibly in the liver or the brain, or almost anywhere in the body.

What shall we expect to find in relation to this ear? We are not given much detailed information. All we know is that the patient had had a discharging ear for a long time. He also had diabetes and cirrhosis and low resistance, however, and I suspect that this septic process was extending inward and that it had something to do with the later illness. I assume that he had involvement of the internal ear or that he had an abscess, possibly extradural or in the brain. He did not have meningitis, because the spinal fluid was normal. On the evidence at hand we cannot exclude the possibility of brain or extradural abscess or lateral sinus thrombosis. This is merely speculation, but these are the conditions that are apt to occur from chronic suppurating ears.

Finally, the illness was associated with a *Staph. aureus* infection of the blood stream, which I believe was localized in the heart valves — certainly the aortic and possibly the mitral.

Did the patient have any other disease, such as a superimposed kidney lesion of some sort? He retained a tremendous amount of fluid during the last few days, and in that retention of fluid there may have been several elements. He probably had some degree of portal obstruction that encouraged ascites. He may have had some cardiac failure, although the clinical picture was not characteristic, as well as a kidney condition that encouraged the retention of fluids. The urine showed white cells, red cells and casts, but no albumin. There are at least three types of disease that might be found in such a case. A diffuse glomerulonephritis, which is the first type, almost always shows large amounts of albumin. The other types are the changes of intercapillary glomerulosclerosis and abscesses from staphylococcal septicemia.

The diagnoses that I suspect may be found are cirrhosis of the liver (Laennec type), diabetes mellitus, chronic suppurative otitis media, staphylococcal septicemia, bacterial endocarditis, embolic abscesses of the kidney or other organs, possible lateral sinus thrombosis, possible brain abscess and possible glomerulonephritis.

Clinical Diagnoses

Portal cirrhosis.
Hemochromatosis?
Staphylococcus aureus sepsis.

Dr. Townsend's Diagnoses

Cirrhosis of liver, Laennec type.
Diabetes mellitus.
Otitis media, chronic suppurative.
Staphylococcal septicemia.
Bacterial endocarditis.
Embolic abscesses, of kidney or other organs.
Lateral sinus thrombosis?
Brain abscess?
Glomerulonephritis?

Anatomical Diagnoses

Acute bacterial endocarditis (due to Staphylococcus aureus), *with rupture of aortic valve.*
Hemochromatosis.
Bicuspid aortic valve.
Septic infarct of kidneys and spleen.

Pathological Discussion

Dr. Benjamin Castleman: Autopsy showed a number of findings that Dr. Townsend predicted. The heart was enlarged, weighing over 400 gm. The enlargement was probably due to a mild degree of aortic stenosis. There was a bicuspid aortic valve, as well as calcific deposits of a mild degree along both cusps. Superimposed on the deposits of calcium were grayish, pink vegetations — an acute bacterial endocarditis that had perforated both cusps. There was also a small focus of bacterial endocarditis on the mitral valve.

The liver weighed 1200 gm. and showed a severe hobnail type of cirrhosis. The color of the liver was pale brown, verging on orange, which is a color often seen when there are deposits of hemosiderin in the liver, and this was confirmed by a positive Prussian-blue reaction for iron. Although the presence of hemosiderin does not always mean hemochromatosis, a history of diabetes in addition to the finding of a uniformly deep-brown pancreas filled with hemosiderin makes the diagnosis of hemochromatosis quite definite. The pancreas was not extremely fibrous but perhaps more so than normal, and the color was certainly that seen in bronze diabetes; also, many of the regional lymph nodes were brown. We can assume that the patient did have hemochromatosis. We reviewed the original biopsy taken four and a half years previously, and that did not show hemochromatosis. It was a fairly adequate biopsy and revealed definite portal cirrhosis. This is an important case in relation to the pathogenesis of hemochromatosis. Most people believe that the initiating factor in the cirrhosis of hemochromatosis is the pigment — that is, the pigment stimulates fibrosis first in the liver and then in the pancreas. Another theory of the pathogenesis of hemochromatosis is that cirrhosis of unknown cause appears first and the iron from the normal blood destruction is abnormally metabolized. Deposits of iron in the liver were therefore superimposed on a previous cirrhosis. This case certainly fits in with this theory.

Dr. Townsend: Did the other endocrine organs, such as the adrenal glands, show hemochromatosis?

Dr. Castleman: No. The involvement was not so diffuse as that in the usual cases of hemochromatosis. Quite possibly it was not present long enough.

Dr. Townsend: This is probably why the patient's skin had a queer color. He was not given the clinical skin test?

Dr. Castleman: Not by the injection method. It is possible that the biopsy might have shown a Prussian-blue reaction. The kidneys contained hemorrhagic septic infarcts.

Dr. Townsend: The kind that occurs with *Staph. aureus*?

Dr. Castleman: Yes. Two small infarcts in the brain accounted for most of the cerebral symptoms.

Dr. Townsend: Was there any local disease around the ear?

Dr. Castleman: No; there was no severe involvement of the middle ear, and no sinus thrombosis.

CASE 32482

Presentation of Case

A thirty-four-year-old unmarried woman, a typist, was admitted to the Neurological Service because of severe pain in the right leg.

Six months before admission the patient had been operated on because of prolonged excessive vaginal bleeding of two months' duration; there had been three episodes of severe low abdominal pain during this period. At operation both tubes and bloody cysts of both ovaries were removed. Fifteen days after operation a sudden, severe right-sided "sciatica" had occurred, after which the pain had been constant. It ran from the hip into the right leg, down to the heel and sometimes up the spine. Between the severe, sharp bouts it was present as an ache. At the time of the menstrual periods, the pain was worse. It was not aggravated by coughing, sneezing or straining. X-ray studies of the chest and hip were negative. After operation there was no intermenstrual bleeding. The periods were regular and extremely painful. The pain was largely in the left lower quadrant. The distress made the patient nervous and apprehensive, and she was often nauseated. She had lost 5 pounds in weight.

Physical examination showed an undernourished and anxious woman. There were tenderness and voluntary spasm in the left lower abdominal quadrant. The right leg was slightly weaker than the left, and straight-leg raising was limited to 45° on that side. The cervix was large and soft. The uterus was retroverted, partially fixed and enlarged. Any movement of the cervix or uterus caused severe pain. A cystic mass was palpable in the posterior cul-de-sac. Rectal examination confirmed the fixation of the uterus and the presence of a hard mass off the left side of the cervix and uterus.

Examination of the blood revealed a red-cell count of 4,010,000, with a hemoglobin of 12.6 gm., and a white-cell count of 8600. The urine gave a + test for albumin, and the sediment contained 3 to 30 white cells and 1 red cell per high-power field. The sedimentation rate was 2 mm. in fifteen minutes, 7 mm. in thirty minutes, 14 mm. in forty-five minutes and 19 mm. in sixty minutes. X-ray studies of the chest, spine and kidneys were negative. In the intravenous pyelogram the lower ureters diverged

somewhat laterally, and there was pressure on the superior margin of the bladder, probably from an intrapelvic mass, which could not be outlined.

An operation was performed on the fifth day.

Differential Diagnosis

Dr. Marshall K. Bartlett: There are a number of points of interest in this history. In the first place, of course, one would like to know the nature of the ovarian cysts removed six months before entry. What kind of lesion could have caused the surgeon to remove both tubes and bilateral ovarian cysts in a thirty-four-year-old unmarried patient? Simple cysts of the ovaries might contain bloody fluid and give the type of vaginal bleeding that this patient had. The duration of trouble before the first operation was brief, but there was no previous mention of dysmenorrhea. We know that there were three episodes of severe pain low in the abdomen during that period. Were the cysts endometriosis? That certainly comes to mind promptly in an unmarried patient of thirty-four who has menstrual difficulties. Were they malignant cysts? I think that we can go far enough to say that if they were malignant the fact was not recognized at the time of operation; otherwise, that type of procedure would not have been done. Certainly, removal of the cysts and the tubes would not be considered adequate surgery if the lesion had been recognized as malignant. I do not see how we can decide the exact nature of the cysts.

The next thing of interest is the onset of severe right-sided "sciatica" fifteen days after operation. Was that due to an underlying lesion in the pelvis? It is hard for me to accept that as the principal cause. It seems to me that if this had been a development of a process in the pelvis the onset would have been more gradual and more insidious. The distribution suggests involvement of the sacral nerve roots. The pain was continuous, with acute exacerbations throughout the interval, until admission to the hospital. It is stated that the pain in the back and leg was worse at the time of the periods. I cannot attach too much significance to that, because almost every patient with backache asserts that it is worse at the time of a period; I am therefore inclined to discount the statement.

X-ray studies of the chest and hip were negative. The periods were regular, with no further intermenstrual bleeding. In other words, normal ovarian tissue must have been left behind at the operation — at least enough so that the patient was able to have regular periods. The periods were painful. Again, it would be interesting to know how much dysmenorrhea she had had before the first operation. In any case, in the interval between the two operations, the periods were painful, and the pain was chiefly in the left lower quadrant. On admission it was noted that the right leg was slightly weaker than the left. One would like to know if that muscle weakness was generalized, involving all the muscle groups, or perhaps limited to certain muscle groups. Certainly at that time there was a pelvic lesion of some kind, with a palpable mass. Was the original lesion a pelvic inflammation and was this episode a recurrence? It seems unlikely to me, because the tubes had been taken out at a previous operation for pelvic inflammation. That should have cured her. Were the cysts that were removed simple ovarian cysts? Again, it seems to me that the patient should have been cured by the first operation and should not have gone on to develop a further pelvic lesion, or at least not so promptly. Were they malignant ovarian cysts, with recurrence in the pelvis? I do not see any way that I can rule that out. She was rather young, which is somewhat against it. I think that if the disease had been recognized as malignant she should have had more extensive surgery at the original procedure.

Could recurrence of malignant disease in the pelvis cause the back pain? I think that it could on the basis of metastases. We have no x-ray evidence to support that. Could this process in the pelvis have been endometriosis? Certainly, the patient was in the right age group. She was nulliparous and it seems like a good bet. If the first operation was done for that reason, a conservative procedure would be justified in a patient of her age, although the removal of the tubes, of course, would not be desirable. It would account for the recurrent process in the pelvis with dysmenorrhea in the interval between operations. Can we explain the back pain on that basis? I cannot remember seeing a patient with back pain of this type due to endometriosis. I am rather inclined to believe that the back pain had no relation to the process in the pelvis. As my first diagnosis, I shall put endometriosis as the cause for the underlying disease, with a malignant lesion in the pelvis as a second choice.

Dr. Tracy B. Mallory: Dr. Ingersoll, you were present at the operation, will you describe the findings?

Dr. Francis M. Ingersoll: I was not present, but I heard about it. The patient had been operated on previously. At operation the surgeon found what can best be described as a "frozen pelvis" — so frozen that operation was a difficult technical procedure. Behind the sigmoid on the left side, there was a cystic mass and the sigmoid mesentery formed one of its walls. In freeing up the sigmoid three holes were made in it, which I mention simply to demonstrate how difficult it was to free the sigmoid and straighten out the situation in the pelvis. There was a cyst not related to the ovary on the right side. Since it was apparent that an extensive endometriosis was involved, the surgeon removed the uterus and the remnants of the ovaries and did a colostomy, exteriorizing the sigmoid.

Clinical Diagnosis

Endometriosis.
Pelvic inflammation?
Carcinoma of ovary?

Dr. Bartlett's Diagnosis

Endometriosis.

Anatomical Diagnosis

Endometriosis.

Pathological Discussion

Dr. Mallory: The specimen that we received in the laboratory showed extensive endometriosis of the remaining fragments of the two ovaries and of the posterior surface of the uterus. There is very little doubt that the wall of the sigmoid would have shown the same process if we had received a specimen from it. These cases of endometriosis involving the sigmoid often make a difficult surgical problem. In a certain number of cases the surgeon has mistaken the lesion for a primary carcinoma of the bowel and has done extensive resection. In cases in which the lesion has been correctly diagnosed at operation, it has frequently been possible with a colostomy to tide over the temporary intestinal obstruction, perform a surgical castration and later take down the colostomy and find that the intestinal obstruction has been relieved. The endometriosis atrophies spontaneously once the ovarian function has been destroyed.

Dr. Bartlett: Do you know what caused the pain in the back?

Dr. Howard Ulfelder: The patient is much better, but of course she has been on bed rest since the operation.

A Physician: Is it possible to explain the pain on the basis of pressure on the ureters?

Dr. Mallory: It was impossible at operation to recognize either ureter. Both ureters were buried in scar tissue and may well have been involved, although that would have been an unusual reference of pain, would it not?

Dr. Ulfelder: I should think so.

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INCREASE IN MORBIDITY DUE TO DIPHTHERIA

A note from the Massachusetts Department of Public Health, appearing elsewhere in this issue of the *Journal*, indicates that there has been a marked increase in diphtheria in Greater Boston during 1946, a considerable portion of which has occurred since September 1. In recent years diphtheria has become a rare disease in Massachusetts, and during the past decade many physicians have not even had the opportunity of studying clinical cases during the time of their medical-school training. Control of this infection has been attributed largely to immunization programs that have been universally adopted throughout the Commonwealth.

Preliminary laboratory reports have demonstrated that the diphtheria bacilli recovered from many of the cases in the Greater Boston area during September were the gravis type. Studies published in 1943 suggested that such strains are associated with a malignant variety of clinical diphtheria with a considerable proportion of infections of the so-called "bull-neck" variety,[1] but this observation has not been confirmed in Massachusetts.[2] Thus, in a recent outbreak from which the gravis type of diphtheria bacilli was recovered, the majority of cases had an extremely mild clinical course. This confirms the conclusion of Frobisher[3] that clinically severe diphtheria is only irregularly associated with the gravis type of organism, which is not of itself sufficient to cause malignant diphtheria.

In Canada recent statistical studies have indicated a change in the age distribution of diphtheria, and in one reported epidemic it was found that 45 per cent of the cases occurred in persons over fifteen years of age.[4, 5] In Massachusetts, during 1945, 44 per cent of the cases were in the same age group, and in the three preceding years, at least 45 per cent of all reported cases occurred in persons who were ten or more years old.[2]

Another interesting observation noted in the Canadian report is that 250 (24 per cent) of 1028 diphtheria cases occurred in persons who had been completely immunized or had negative Schick reactions. It was also found that 9 persons developed diphtheria who had a circulating antitoxin level in excess of the Schick-negative level of 0.004 unit per cubic centimeter; that these persons actually had diphtheria is indicated by the fact that they developed a significant increase in antitoxin titer after convalescence. In another study, however, a comparison of the incidence rates in two groups — one composed of Schick-negative persons and the other of unimmunized persons — showed that the rate in the Schick-negative group was one tenth of that in the unprotected population. In a preliminary tabulation of 99 cases recently reported in and about Boston, it was found that 25 persons had been previously immunized, 5 of these patients having received their inoculations since 1944 and 15 since 1940.

The present tendency toward a shift in the age distribution of diphtheria cases and the occurrence of the disease in a large proportion of immunized persons are of particular significance when consideration is given to the question of booster doses. For several years, the Massachusetts Department of Public Health has advocated booster doses for children at the time of entering school. In the Greater Boston area, in the face of the increased incidence, it is now recommended that booster doses be administered to all preschool children if two or more years have elapsed since the time of the initial inoculation — on a community basis, it is perhaps more practical to administer a booster dose of toxoid than to do Schick tests and to inoculate those with a positive reaction. Furthermore, boards of health have been advised to intensify efforts at maintaining a high proportion of immunized children. It seems likely that the relative freedom from cases of diphtheria during the past few years has resulted in a relaxation in efforts in this direction. It is apparent, however, that the percentage of immunized persons must be high to prevent the occurrence of cases when the diphtheria organism is introduced into the community. Diphtheria seeks out the unimmunized!

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GIVE THE INTERN HIS DUE

A LETTER published elsewhere in this issue of the *Journal* expresses views on the relations existing between staff physicians and interns in private hospitals. According to these observations the visiting physician considers the "lowly intern as an ornate figure in white that the hospital has hired and stationed as a silent sentry."

The burden of this argument is that the intern is not allowed to help in the care of the visiting physician's private patients except for a certain amount of humble routine work-up, that he is by-passed and ignored when any real responsibility is entailed and is, indeed, "a superlative and superfluous hospital attaché, who must of necessity be allowed to complete his requirements for licensure."

The remedy, our correspondent believes, is for the visiting physician or surgeon to treat his intern with greater respect and to consider him a junior colleague who has his own contribution to make and who will repay the confidence of his senior a hundredfold in co-operation and in eagerness to be of service. Given opportunities to draw on the accumulated experience — perhaps even the wisdom — of his staff physician, the intern will respond with the latest scientific facts acquired in the halls of academic learning, as well as with a loyalty that will be reflected in improved hospital functioning.

It is surprising to learn that there are presumably up-to-date hospitals anywhere in the country that can pretend to function properly with their interns marking time as superfluous attachés. We hope that there are fewer in existence than our informant believes, and that there are not many practitioners of medicine or surgery who dare to assume full responsibility for hospitalized patients without the complete co-operation of an efficient resident staff. It had not occurred to us that such teamwork could be lacking anywhere to any appreciable extent.

There was formerly an era in which the bulk of medical knowledge was in the possession of the practitioner, who, according to his characteristics, was gracious or otherwise to his hospital interns. Today the shoe comes closer to fitting the other foot: it is the unco-operative attending physician who runs the risk of being by-passed by his house staff if he does not recognize and appreciate the services that are usually available to him and can hardly be obtained otherwise.

MASSACHUSETTS MEDICAL SOCIETY

COMMITTEE TO SURVEY MALPRACTICE INSURANCE IN MASSACHUSETTS

All those who have not as yet completed and returned their questionnaires regarding medical malpractice insurance are requested to do so *immediately* in order that the facts can be made available to the committee for study. Obviously, all information obtained from the questionnaires will be held strictly confidential.

This is the most comprehensive survey of this type undertaken by the Massachusetts Medical Society, and it is hoped that a 100-per-cent return can be approached.

CARL BEARSE, *Chairman*

A HUNDRED YEARS AGO

It has long been an important problem in medical science to devise some method of mitigating the pain of surgical operations. An efficient agent for this purpose — inhalation of ethereal vapor — has at length been discovered. The process is obviously adapted to operations which are brief in their duration, whatever be their severity, and it may hereafter prove safe to administer it for a length of time and to produce a narcotism of an hour's duration. — We learn that a disgraceful fight took place on Sunday noon last between the Freshmen and medical students of Dartmouth College. It took place as they were leaving the church. — We apprehend that rectum bougies are not resorted to as frequently as they might be with striking manifestations of advantage to the patient. There is a fashion to be followed in the treatment of chronic diseases as well as in the cut of a coat. The surgeons of thirty years ago derived much more assistance from these very instruments, though of inferior manufacture, than their successors of the present day. — It is spoken of as a matter already settled that Dr. Wm. Lawrence of Boston, who has lately returned from Europe, has purchased the old Medical College in Mason Street which is to be fitted up for an Infirmary for children and infants. — On Wednesday last, the new edifice of the Medical College near the Massachusetts General Hospital in Grove Street was formally opened by an address from the President of Harvard University, who was particularly happy in his remarks upon the social position of medical practitioners, their duties, and their philanthropic exertions. Every person present must have been gratified with his observations, clothed as they were, in beautiful language. — If students of medicine are not well taught in this age, there must be some defect in themselves. It is a subject of perfect surprise to us that a single stupid fellow can be found in a lecture-room or office, surrounded as he must be continually by an atmosphere of science. — A boy aged 7 years received a wound between the 7th and 8th ribs by a thrust from a narrow but long-bladed knife. Three weeks and four days from the accident, he was taken with a sudden and fatal syncope. A cicatrix of the size and form of the knife-blade was found on the pericardium. There was an opening in the anterior coronary artery. The patient would have recovered perfectly if sloughing of the coronary had not taken place. Such cases do recover in all probability. We hear of cases where buffaloes have been killed, and rifle or musket balls found lodged in the substance of the heart; having entered a long time previous to death. — A slave recently died at Frankfort, Ky., at the age of 112 years. When 84 years of age, he married his fourth wife, and raised a family of 7 children. — Another important discovery has been made in the manner of preparing gold for dental purposes. Dr. Charles T. Jackson, a gentleman who takes the first rank in chemistry, has prepared pellets of pure gold, almost as flocculent as wool, which only require a slight degree of manipulation to fit them to the ragged interior of a tooth, without pain, and with so slight a pressure as to make no disturbance in the region. Those who have borne the heavy pressure of the dental operator's punches and the fatigue of being belabored scientifically to save a few diseased teeth will welcome the new process with marked pleasure and interest. — An Aesculapian Society, entirely made up of medical students attending lectures in New York has commenced weekly sessions for the season. — Extracted from the *Boston Medical and Surgical Journal*, November, 1846.

R. F.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

DIPHTHERIA ON THE INCREASE

Recently the Boston Health Department, in a letter addressed to physicians in Boston, pointed out that there has been an increase of diphtheria cases in that community. A similar and more striking rise has been noted in the adjoining community of Somerville. Diphtheria case rates for the two cities since 1940 are shown in the following table:

Year	Boston	Somerville
1940	2.075	9.786
1941	2.075	2.936
1942	2.075	7.829
1943	4.670	17.616
1944	6.486	45.998
1945	5.967	20.552
1946 (8 months)	9.470	26.424

The case rates are per 100,000 population, based on 1940 United States Census.

Since January 1, 1946, a total of more than 161 cases have been reported in the Greater Boston area, and 79 of these have occurred in Boston and Somerville during September and the first eleven days in October. It is expected that cases will continue to appear at an increased rate in this area until the effect of intensified diphtheria immunizations will have become manifest. The letter suggests that physicians bear in mind the possibility that diphtheria may occur more frequently now than it has in the past. Delay in diagnosis and tardy administration of antitoxin have been factors in the fatal outcome of several cases.

The increased incidence has been called to the attention of all boards of health in the Greater Boston area, with the recommendation that diphtheria immunization programs be strengthened. Booster doses for children previously immunized are being suggested in Boston, Somerville and the adjoining communities.

It is impossible to predict the area in which the disease will appear next. For this reason each community in the Commonwealth is being warned to take stock of its diphtheria immunization program, with immediate steps to forestall a similar rise in prevalence. The regular immunization program is as follows:

1. Primary immunization of all children in the first year of life — three doses of diphtheria toxoid (0.5, 1.0 and 1.0 cc.). Any children not immunized then should be given toxoid at the earliest opportunity.
2. A booster dose (0.5 cc. of toxoid) at entrance to school if primary immunization was done more than two years previously. The same booster dose for children in grades up to high school who did not receive a booster dose on entrance to school in previous years.
3. If high-school children or adults are to be immunized a Schick test should be performed. Susceptibles should be given toxoid in divided doses, beginning with 0.1 cc. Routine booster doses are not recommended for adolescents and adults. Combined diphtheria-pertussis and combined diphtheria-tetanus immunizing agents can be used for primary immunizations and for booster doses. These products are not yet available through the department.

In the present emergency it is recommended that a booster dose be given to all preschool children if more than two years has elapsed since primary immunization.

CONSULTATION CLINICS FOR CRIPPLED CHILDREN IN MASSACHUSETTS UNDER THE PROVISIONS OF THE SOCIAL SECURITY ACT

Clinic	Date	Clinic Consultant
Salem	December 2	Paul W. Hugenberger
Haverhill	December 4	William T. Green
Lowell	December 6	Albert H. Brewster
Greenfield	December 9	Charles L. Sturdevant
Gardner (Worcester subclinic)	December 10	John W. O'Meara
Springfield	December 10	Garry deN. Hough
Brockton	December 12	George W. Van Gorder
Pittsfield	December 18	Frank A. Slowick
Hyannis	December 19	Paul L. Norton
Worcester	December 20	John W. O'Meara
Fall River	December 30	David S. Grice

Physicians referring new patients to clinic should get in touch with the district health officer to make appointments.

MISCELLANY

NOTE

The appointment of Dr. Hugo Muench, a former staff member of the International Health Division of the Rockefeller Foundation and professor of biostatistics at the Harvard School of Public Health, as head of the Department of Biostatistics, was recently announced by Dr. James S. Simmons, dean of the School. Dr. Muench is also assistant dean.

FURTHER EVIDENCE CONCERNING THE DANGERS OF DEMEROL

An editorial in the August 8 issue of the *Journal* called attention to the dangers of addiction following the use of Demerol, an article by Paul De Kruif in the June issue of *Reader's Digest* notwithstanding. Further evidence of the habit-forming possibilities of the drug is given in a letter "Experience with Demerol in Europe," by Dr. Max Samter, of Chicago, which was published in the September 28 issue of the *Journal of the American Medical Association*. It is reprinted below to re-emphasize the dangers that may result from the use of this drug.

To the Editor: — The following observations may be of interest to you with regard to the controversy between Dr. C. K. Himmelsbach, Chicago, Mr. H. J. Anslinger, Washington, D. C., and Paul de Kruif, Ph.D., Holland, Mich. (THE JOURNAL, September 7).

In the spring of 1945 I acted as liaison officer between First Army Headquarters and a central "German Sanitary Staff" established temporarily to maintain the function of the large number of captured German medical installations. Repeated inspections of hospitals and numerous trips throughout the occupied area gave me an opportunity to become familiar with administrative and technical experiences and difficulties encountered by the German army.

A tragic accident led me to investigate the use of Demerol by the medical department of the German units then under our control. Allied troops which had opened a medical depot found a large stock of an alcoholic preparation of Dolantin (the German trade name for Demerol), mistook it for a beverage and drank numerous bottles; a large number of casualties resulted.

Consultation with German medical officers and pharmacists revealed that the staff had at this time 40 cases of known Demerol addiction in its files; that, furthermore, a large number of hospitals had abandoned its use for this reason. It is interesting to note that in Germany too it had been assumed for some time that Demerol was less addicting than morphine, a theory which had been revised by the spring of 1945.

Subsequently I was called repeatedly by military government officials to examine cases of Demerol addiction in civilians. I remember 1 instance which illustrates convincingly the danger of the drug. A physician addicted to morphine submitted twice to treatment. After the second treatment he was advised to try Demerol and developed within three months an addiction to the substitute. During this period he performed an abortion and was committed to a sanatorium for clinical study. After several weeks an attempt to withdraw the drug was made; he developed no symptoms of withdrawal. It was suspected, therefore, that he had managed to obtain considerable quantities of the drug. Careful isolation revealed not only that his wife in weekly visits had issued Demerol to him but that she herself — after having taken the drug once or twice as a sedative, following her husband's confinement — had become a Demerol addict.

Although the case histories on pages 43 and 44 of the September 7 issue of THE JOURNAL contain convincing evidence against Paul de Kruif's statement, it might be helpful to add these experiences to the warning.

MAX SAMTER, M.D., Chicago

CORRESPONDENCE

THE HOSPITAL INTERN

To the Editor: Everyone concerned in the patient-doctor-hospital relation stands to gain by a more cordial affinity between staff physician and intern. The visiting physician seems to have become inured to the lowly intern as an ornate figure in white that the hospital has hired and stationed as silent sentry. Instead of taking full advantage of an enthusiastic scholar fresh from the portals of medical learning, the intern is by-passed in the doctor's care of private patients and completely deleted from their management. Both are the losers in such an aloof and lowly arrangement. Hence, the intern's year often passes without the establishment of close contact with the physician, for which he yearns and is justly entitled. He is allowed to pursue his tenure in white as a superlative and superfluous hospital attaché, who must of necessity be allowed to complete his requirements for licensure.

One junior colleague's choleric comments aptly reflect a general attitude. In being brushed aside by the doctor and patient as well, he sputtered: "Nuts to them. If I'm not good enough for him or his patient, I'll sit my year out until I'm good enough for patients of my own." And he quickly added, "He can do his own scut work; he'll not get any more out of me than I have to give."

The intern is in a logical position to lighten the load of routine for the staff physician's hospital practice. For example, a convenient plan, followed by some, is to make the acquaintance of the intern at the beginning of his month on the service. During a friendly chat the intern is made cognizant of one's type of practice and exactly what is expected. He is made to believe that the doctor's success is, in part, directly dependent on him. As a junior partner, his ability is equally important to the older man's skill in patient management.

One method of giving the intern concrete information is handing him at this time a small card on which are recorded routines, orders and special idiosyncrasies that the staff man may have. Such a fraternal display of friendliness will win over any intern to his staff man, making him a willing understudy and servant. After such an initial relation the intern takes a personal interest and responsibility in each patient.

He is given the information necessary for leaving initial orders should the chief be unavailable; he calls for special orders and advises of the patient's admission status.

Added to this time-saving factor of relieving the staff man of admission orders are meticulous work-ups and accurate diagnoses. By thus taking the intern under his wing, the physician ensures these; his understudy does not wish to have faith broken in him when once it has been entrusted. Instead of a *laissez faire* attitude in his intern, the chief will note a thorough, conscientious one with precision in examinations. The intern may find items that the staff physician, in the hurry to get the patient hospitalized, has casually overlooked — physical findings of inestimable value in the case or precautionary measures that may obviate complications. In reality, an attending man's reputation lies in the hand of the intern. It is enhanced by the loyal junior, whose enthusiastic remarks to the patient regarding the excellent care his doctor renders ensure respect and reliance.

Hospital rounds can be expedited by the intern. Nothing is more flattering to the intern than to have his senior walk up on the floor and ask, "How are *our* patients, today, Doctor?" After this show of complete confidence that the intern has seen his patients and taken a personal interest, the response will be prompt. A recital of important changes or any complications needing the physician's special care will be on the tip of his tongue. Or if all is well, he will say, "Mrs. so-and-so is doing beautifully. If you are in a hurry she need not be seen today."

While in medical school, the intern learned his clinical medicine at the feet of astute professors. Their diagnostic acumen and teaching finesse firmly implanted didactic facts in his mind. He knelt at their feet four long years, listening to the masters and longing to emulate their skill. On entering the hospital he realizes that much of his knowledge is theoretical. He is anxious to see and treat patients and to prove from experience — theory is fact. He looks appealingly to the visiting staff to be his teachers. His fire for knowledge, however, may be deplorably smothered by the cold-shouldering staff man, who assumes a "better-than-thou" attitude and treats him like something akin to a floor mat.

The doctor may appropriately take his superior place as clinical instructor. The intern is crying for teaching. He considers his internship worthwhile if an occasional chief drops a few pearls from the treasure chest of experience. And it is not beyond the realm of possibility that the junior will be able to reciprocate with a few kernels of gold — nuggets recently pocketed in medical school and facts that may be useful in practice. New therapeutics are fostered by interns and residents, as well as tried and proved by them.

In payment for instruction, the intern will dig through the cumulative index for some article that his chief would like and will abstract it for him. He will graciously spend hours in diligent search for the latest treatment of a patient with chronic arthritis.

Psychotherapy, if indulged at all, can devour the lion's share of any doctor's time. In fact, time is so limited on hospital rounds that such therapy is prohibitive. Either it is deleted from the patient's care or a psychologist is called in. Here the loyal intern can shine. It would be sheer naïveté to allow an intern to approach the nervous patient without previous introduction and instruction by the patient's family physician. But after such a status is attained, the "man in white" can render suave, persuasive psychotherapy by proxy for his chief. He can give patients encouragement and inspire confidence to hasten recovery and can thus save many hours of tedious tongue trilling, at the same time giving the patient an added service that not otherwise would have been received.

If a practice is a bit too large for one man to handle and a new man is needed, a fertile field from which to choose an aide comprises the young, red-blooded, hospital interns. And there is no better way to select one than to observe various interns in their care of patients. By permitting them the freedom an assistant enjoys, the staff man sees how responsibility is borne. In this way a partner may be chosen who clicks with colleague and patient. Meanwhile, the heavy burden of routine is lifted from the senior man's shoulders; his attention can be devoted to critical patients.

A pet peeve of the junior man in the operating room is the "eager beaver" surgeon — the one in such a mad rush to earn his first million dollars that he never allows the intern to do anything but hold retractors or get out of his way. If the surgeon believes that the preoperative and postoperative care of his patients is sometimes not just what it ought to be, perhaps there is a reason. If he permits the intern to consider himself an integral part of the surgical team, not an ornament or a modified scrub nurse, he will soon note remarkable improvement in the intern's interest in the postoperative course of patients.

Whenever the intern performs a procedure, minor though it be, he tacitly assumes that the patient is his own. He did something for the patient; therefore, he is obligated to care for his patient, and he is appreciative for the surgeon's generosity. He repays by close watch over postoperative patients. Menial chores are cheerfully performed, intravenous injections gladly given, dressings changed and wounds observed with special care, since one of his own sutures may have gone into the handiwork of that operation.

The intern does not ask for the surgeon's knife, but merely for an opportunity to learn a little surgical technic and the privilege to get the feel of things at the operating table — the chance of tying a few knots, snapping on hemostats, closing skin incisions and performing minor procedures under supervision. Such small gestures of confidence in the intern do take a little extra time on the part of the surgeon. But the time is well invested. It will pay big dividends in the care of surgical patients.

Small favors shown the intern not only will make for better intern training but also will simultaneously lighten the load of the staff doctor. The loyalty of the intern to his staff man and hospital will be reflected in more pleasant and more efficient hospital management. Most important, the patient will reap rich rewards in greatly improved hospital care, and his esteem for doctor, intern and hospital will increase accordingly.

LIEUTENANT J. DE WITT FOX, M.C., A.U.S.
Brooks General Hospital
Fort Sam Houston, Texas

INTRODUCTION OF DIGITALIS INTO NORTH AMERICA

To the Editor: A New Hampshire physician first used *Digitalis purpurea* in North America. Hall Jackson (1739–1797) lived in Portsmouth and was well known in New England. His father, Clement Jackson, was a doctor, and from him Hall received his early medical education. For three years he attended lectures in London at the public hospitals and made many friends there. At that time his principal interest was in smallpox. He returned to the colonies, and in 1764 he was called to Boston because of a smallpox epidemic. Later he opened a smallpox hospital on Henzell's Island. Five days after the Battle of Concord he offered his services in raising a company of Minute Men. On June 19, 1775, he was again summoned to Boston to take care of the wounded from the Battle of Bunker Hill, and he later became surgeon of a regiment that fought through the Ticonderoga Campaign. In November, 1775, he was appointed chief surgeon of all New Hampshire troops in the Continental Army, with the rank of colonel.

His interest in digitalis dated from the reading of William Withering's treatise, which he had received from London. Enthusiastic over the results that Withering had obtained, he sent to London for some of the powdered leaf and used it on his own patients. His results were so good that he wrote to Withering to tell him. Withering responded by sending him some of the seeds to be planted in New England. He suggested that the seeds be sent to other physicians in the states.

Jackson's first letter to Withering is now in possession of the Royal Society of Medicine, London, whose librarian, Mr. G. F. Home, has kindly allowed its use in this note. It reads as follows:

Portsmouth, New Hampshire
North America
February 9, 1786

Sir,

Your inestimable treatise or account of the Foxglove and its medical uses: with practical remarks on dropsy, and other diseases, has found its way to this remote part of the globe. It must greatly add to the satisfaction that daily arises in your mind, on seeing so many

distressed fellow-mortals relieved by your personal advice, and administrations, to reflect that thousands at the most distant ends of the earth, are wishing to offer their tribute of gratitude for your indefatigable endeavours for the good of mankind.

The gentlemen of the Society of Medical observations, and enquiries, in London, the ingenious and worthy Doctors, Percival and White, of Manchester, with many others, of this day, in England, will never know how much the world is indebted to them for their publications; not only the present age, but generations yet unborn will bless their memory.

There is no disorder more prevalent in this country than dropsy, our summers are extremely hot, our winters intensely cold; only two of the spring and fall months may be called temperate; our days in the winter are short, consequently our labouring people work but a few hours, the remainder of the time is spent in a sedentary, idle manner, and too often in an immoderate use of spirituous liquors: Our lumber trade to the West Indica Islands, returns in large quantities of rum and Molasses: of the latter is distilled amongst us an inferior, cheap kind of rum, which is evidently unwholesome, it is generally used immediately from the still, it has an empyreumatic taste, and is wholly destitute of the mildness of rum that has undergone agitation at sea, and a few months age; a common labourer may receive five quarts of this new, strong, and fiery spirit, for a short day's work, from this plenty and cheapness the use is too general, and immoderate, and it is a just observation that those who indulge too freely in the use of spirits, are least anxious for substantial food. Their appetites are palled, the solids weakened, the fluids irritated, and increased, obstructions formed, and dropsies become frequent. As yet no specific reason has been found, but in most cases, after a longer, or shorter time, the disease has proved mortal: Life in many cases has been prolonged to a considerable length of time by repeated tapping, but this has generally been with female subjects, where the disorder was of the encysted [*sic*] kind. Our remedies in general, have been such as are used in Europe, in like cases. The squills have been considered as the most powerful diuretic, and mostly depended upon, and some few have been relieved by their use, where resolution has been strong enough to preserve against the nauseating effects thereof.

I have taken your treatise in my pocket for six weeks, I have shown it with the incomparable, accurate, and elegant drawing, to all my acquaintance within twenty miles, but no one can recollect of ever seeing any of its kind, in America; I am persuaded however, that it would arrive to sufficient maturity in this country, but attentive cultivation as our natural productions in general, are much the same as those of England, with this difference, the wood of our large trees is not so compact and hard, our fruit trees, nor the fruits, so large, smooth, as those of the same kind, in Great Britain; our plants and herbage in general are a degree, or two, inferior to those in England, planted in equal good soil, and cultivated with equal attention, chamomile will not flower in this country, tho' I have seen, in a very favourable season, a few scattered single-flowers, in a large bed: These remarks are from my own observations, having spent the year 1762 in England for the advantage of medical improvements.

I have the honor of being acquainted with John Lane, Esq., Merchant in London, to him I have sent for a small invoice of medicines; I have directed a small quantity of *Fol. Digitalis Purp*: *Siccat*:, also some of the powder, and seeds, but I greatly fear they have not as yet become articles of the shops, in London, would I be so fortunate as to obtain (to the care of Mr. Lane) thro' your influence, and direction, a small quantity of the genuine seed, the plant should be most attentively cultivated, most carefully prepared and as opportunity will not be wanting to administer it, the most accurate observations and remarks, on its operation, and effects, shall be noted, and if you will permit me the honor, shall be communicated to you, for any further satisfaction, or remarks, you may wish to make on this truly valuable discovery.

And now Sir, I should be most painfully embarrassed for an apology in troubling a gentleman of your character with so lengthy, and uninteresting a letter, without the least personal knowledge, or the remotest introduction, was I not assured that where so much merit, and goodness obtains, an indulgent candour will not be wanting toward one who is sincerely desireous [*sic*] of doing all the possible good, in the narrow sphere in which providence has placed him, and hoped not altogether from those motives that too often actuate the generality of mankind.

I am Sir (tho' unknown) with
the utmost veneration of respect
Your most obliged, most obedient
HALL JACKSON

P. S. I have directed to be sent me two or three sets of your account of the Fox-glove, for the purpose of dispersing them. Also your Scarlatina anginosa, outlines of Mineralogy; and anticipate with great pleasure your promised Botanical Arrangement. Hope it will be published before my directions are completed and sent out from London. The extremes of heat and cold in this country may be judged from the following:

The Thermometer, Fahrenheits' scale stood as followeth:

Portsmouth 1785	July	5th	.....83°
		15th	.....75°
		30th	.....80°
August from the 15th to 30th			.....80°
1786 January — 15 to 19			..... 8° below 0

N. B. The Thermometer was placed in the open air, and the observations made at noon.

The text of Withering's reply to Jackson's letter is not available, but Jackson quotes from it in a letter to Ezra Stiles, which appeared in the January, 1787, issue of *The American Museum* and reads as follows:

Portsmouth, (N. H.) April 30, 1787.

Sir,

In the year 1785, that justly celebrated botanist, Dr. William Withering, physician to the general hospital in Birmingham, Great Britain, published a treatise on the *Digitalis Purpurea*, (Fox-glove) and its medical uses, with practical remarks on dropsies and other diseases. This valuable treatise came into my hands the same year; it contains more than a hundred and fifty cases of dropsies, many of them of the worse and most complicated kind, cured or relieved by this efficacious plant. I last year received from London, a small quantity of the dried leaves, and some of the same in powder. From repeated trials here, I am fully persuaded, that neither Dr. Withering, nor his numerous correspondents, have exaggerated its salutary effects; it is, perhaps, the most powerful *diuretic* in nature, and possesses a remarkable quality of abating the acceleration of the heart, and retarding the circulation of the blood.

By the last ship from London, and last post from Boston, I was honoured with a very polite, obliging, and interesting letter from Dr. Withering, and favoured also with a quantity of seeds of the Fox-glove by him. He writes, "I send more that you will distribute them into other states."

It is with much pleasure that I comply with the doctor's humane wish, in enclosing you a small quantity of them, being fully persuaded you will find equal satisfaction in the cultivation of so useful and ornamental a vegetable; it bears a beautiful purple bell-flower, worthy a place in any garden.

I take liberty of transcribing two other passages in the doctor's letter, which, I think, may, with propriety, accompany the seed. "I am more and more convinced, that the *Digitalis*, under a judicious management, is one of the mildest and fastest medicines we have, and one of the most efficacious. I believe it is not necessary to create a nausea, or any other disturbance in the system. I never use more than 1 *scruple fol. suc.* ½ lb. of infusion, and in substance rarely more than 3 *grains* in twenty-four hours." . . . "*Digitalis* has cured two other cases of insanity in this neighborhood, and three cases of *hemoptae*; the latter were of a kind attended with a quick bounding pulse, and I directed the medicine, from the quality I knew it possesses of abating the actions of the heart."

I would just mention, that it is a biennial plant, and I conclude it will take some little care to preserve the roots from the severity of the frosts in this cold climate, though it flourishes spontaneously in the fields of England.

My good intention must be my apology in the liberty I have taken in troubling a gentleman of your character with so lengthy a letter, altogether professional. I wish to promulgate so valuable an acquisition in medicine, and am so unfortunate as not to be acquainted with any gentlemen of the faculty in your state.

I am, Sir, etc.
HALL JACKSON

The Rev. Ezra Stiles, president of Yale College.

DOUGLAS CARROLL, M.D.

Johns Hopkins Hospital
Baltimore 5

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Essentials of Clinical Allergy. By Samuel J. Taub, M.D., professor of medicine, Cook County Graduate School of Medicine, and attending physician in medicine, Cook County Hospital. 8°, cloth, 198 pp., with 16 plates, 2 figures and tables. Baltimore: The Williams and Wilkins Company, 1945. $3.00.

This manual is written for the general practitioner and medical student. The author has attempted to present a practical clinical approach to the various allergic diseases, as seen in practice. Theoretical discussions have been avoided, and the importance of a broad knowledge of internal medicine is emphasized for the better understanding of allergic conditions. Considerable space is devoted to the discussion of seasonal and perennial hay fever and asthma and to skin disturbances due to allergy. Valuable tables of the pollen flora and pollination dates and skin tests are included in the text. The illustrations of pollen and pollen plants should prove valuable. The final chapter describes various special diets and recipes. This manual should prove of value to the practicing physician.

A Handbook for Dissectors. By J. C. Boileau Grant, F.R.C.S, Ed., M.B., Ch.B., professor of anatomy, University of Toronto; and H. A. Cates, associate professor of anatomy, University of Toronto. Second edition. 12°, cloth, 390 pp. Baltimore: The Williams and Wilkins Company, 1945. $2.50.

The first edition of this manual was written for use in conjunction with *A Method of Anatomy* by the same author. In this edition the handbook has been separated from the latter, all the references to the larger work have been deleted, and instruction for the dissection of every region has been included. The account of the brain is written to meet the needs of the beginner, for whom it should be sufficient. The handbook is designed as an inexpensive guide that students can use without much concern for its ultimate condition but that contains enough information for the identification of any structure met with in the dissection room. It should prove valuable for this purpose.

NOTICES

ANNOUNCEMENTS

Dr. Harry Blotner announces the removal of his office from 189 Bay State Road to 419 Commonwealth Avenue, Boston.

Dr. Joseph Lentine announces the removal of his office from 520 Commonwealth Avenue to 395 Commonwealth Avenue, Boston.

GREATER BOSTON MEDICAL SOCIETY

A meeting of the Greater Boston Medical Society will be held in the auditorium of the Beth Israel Hospital on Tuesday, December 3, at 8:15 p.m. Dr. Shields Warren will speak on the subject "Medical Aspects of the Bikini Experiments." This will be followed by a discussion from the floor.

NEW ENGLAND DERMATOLOGICAL SOCIETY

The regular meeting of the New England Dermatological Society will be held in the Skin Out-Patient Department of the Boston City Hospital on Wednesday, December 4, at 2:00 p.m.

JOSEPH H. PRATT DIAGNOSTIC HOSPITAL

Bennet Street, Boston
Lecture Hall, 9–10 a.m.

MEDICAL CONFERENCE PROGRAM

Wednesday, December 4 — Infections Due to Bacillus Pyocyaneus (*Ps. aeruginosa*): Treatment with Streptomycin. Dr. Malcolm Stanley.

Friday, December 6 — The Present Status of the Peptic Ulcer. Dr. Sara M. Jordan.

Wednesday, December 11 — Xanthomatous Biliary Cirrhosis. Drs. S. J. Thannhauser and H. E. MacMahon.

Friday, December 13 — The Plastic Repair of Burn Wounds. Dr. Malvin F. White.

Wednesday, December 18 — Pediatric Clinicopathological Conference. Drs. James M. Baty and H. E. MacMahon.

Friday, December 20 — Roentgenology in the Study of Heart Disease. Dr. Merrill Sosman.

On Tuesday and Thursday mornings, Dr. S. J. Thannhauser will give medical clinics on hospital cases. On Saturday mornings, clinics will be given by Dr. William Dameshek. Medical rounds are conducted each weekday by members of the staff from 12:00 to 1:00 in the Lecture Hall.

All exercises are open to the medical profession.

Conferences will be discontinued December 24, 1946, through January 11, 1947.

SOCIETY MEETINGS AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING THURSDAY, DECEMBER 5

FRIDAY, DECEMBER 6
*9:00–10:00 a.m. The Present Status of the Peptic Ulcer. Dr. Sara M. Jordan. Joseph H. Pratt Diagnostic Hospital.
*10:00 a.m.–12:00 m. Medical Staff Rounds. Peter Bent Brigham Hospital.

MONDAY, DECEMBER 9
*12:15–1:15 p.m. Clinicopathological Conference. Peter Bent Brigham Hospital.

TUESDAY, DECEMBER 10
*12:15–1:15 p.m. Clinicoroentgenological Conference. Peter Bent Brigham Hospital.
*8:00 p.m. Harvard Medical Society. Amphitheater, Peter Bent Brigham Hospital.

WEDNESDAY, DECEMBER 11
*9:00–10:00 a.m. Xanthomatous Biliary Cirrhosis. Drs. S. J. Thannhauser and H. E. MacMahon. Joseph H. Pratt Diagnostic Hospital.
*11:00 a.m.–12:00 m. Medical Clinic. Amphitheater, Children's Hospital.
*12:00 m. Clinicopathological Conference. (Children's Hospital.) Amphitheater, Peter Bent Brigham Hospital.
*2:00–3:00 p.m. Combined Clinic by the Medical, Surgical and Orthopedic Services. Amphitheater, Children's Hospital.
*7:15 p.m. Graduate Seminar in Pediatrics. Children's Medical Service, Amphitheater 3A, Massachusetts General Hospital.

*Open to the medical profession.

OCTOBER 11–MAY 14. Metropolitan State Hospital. Page 398, issue of September 12.

OCTOBER 15–DECEMBER 5. Exhibition in Commemoration of Ether Centenary. Page 570, issue of October 10.

DECEMBER 3. Greater Boston Medical Society. Notice above.

DECEMBER 4. New England Dermatological Society. Notice above.

DECEMBER 4–20. Joseph H. Pratt Diagnostic Hospital. Medical Conference Program. Notice above.

DECEMBER 5. Suffolk Censors' meeting. Page 346, issue of September 5.

DECEMBER 7–12. American Academy of Dermatology and Syphilology. Page 570, issue of October 10.

DECEMBER 12. Headaches from the Ophthalmological Standpoint. Dr. Edwin B. Dunphy. Pentucket Association of Physicians. 8:30 p.m. Haverhill.

DECEMBER 18. New England Society of Physical Medicine. Page xix, issue of November 21.

(*Notices continued on page xxi*)